EPIDEMIC MYALGIC ENCEPHALOMYELOPATHY

THE DURBAN OUTBREAK

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IN February, 1955, towards the end of a Durban summer, a disease, superficially resembling poliomyelitis, occurred amongst the nursing staff of Addington Hospital (Hill 1955). This is a general hospital of 850 beds, serving the European and Coloured populations of Durban, but not Asiatics or Africans. It is also a training-school for nurses, and, at the time of this outbreak, trained and untrained staff numbered 446. Since a recognised poliomyelitis epidemic was still in progress, the earlier cases were thought to be atypical examples of this condition, but it soon became evident that this was not so. The disease struck with dramatic suddenness, and in one week (Feb. 18–25) 59 nurses became ill. Thereafter, further nurses were affected in the next few weeks (see fig. 1), bringing the total number to 98. An interesting point was the absence of spread to other hospital personnel, or to patients; and this lent support to the suggestion that some toxic substance, common to the nurses' home, was responsible for the outbreak. In this respect, senior practitioners in Durban recalled an outbreak of peripheral neuritis in 1937, which was proved to be due to the use of cooking-oil contaminated by triorthocresylphosphate (Drummond and Macfadyen 1938).

At first the disease was confined to nurses living in, but later many of those who lived out were affected. Moreover, during the month of March sporadic cases were admitted from the city; and this fact, coupled with the failure to incriminate any known toxin, tended to support the theory of an infection.

As the field of investigation was extended, it was suspected that the hospital outbreak was an episode in an infection which had been occurring in the general population for some weeks or even months, and which had remained unrecognised until it broke out with explosive force amongst the nurses. Of the 300 cases of poliomyelitis admitted to Wentworth Isolation Hospital between August, 1954, and February, 1955, at least 37, with normal findings in the cerebrospinal fluid (C.S.F.), were possibly incorrectly diagnosed; and 7 of these, which were subsequently reassessed, displayed minor residual defects which conformed to the pattern of the Addington outbreak.

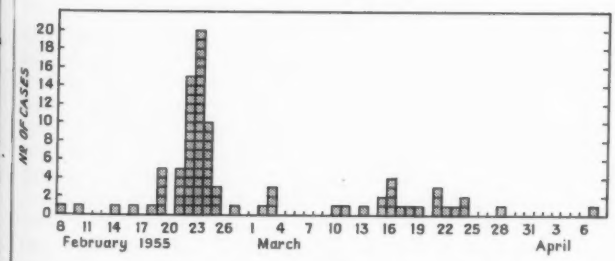

Fig. 1—Dates of onset of illness in the outbreak.

We discuss here the 98 cases at Addington Hospital, mention briefly others among the general public, and refer to similar cases reported elsewhere.

Epidemiology

Full routine investigations were carried out under the direction of Dr. G. D. English, the medical officer of health for Durban, who summarised his report as follows:

"No positive evidence was forthcoming which could throw any light on the cause of this outbreak, and its epidemiology remains obscure. Assuming, however, that it was infective in origin, the incubation period was probably from 7 to 21 days."

Age-distribution

As fig. 2 indicates, of the 98 members of the nursing staff involved, the majority were under 25 years of age, although the ages ranged between 17 and 49. Whilst the attack-rate was highest in the under 25s, the incidence of sequelæ was greater in the older age-groups.

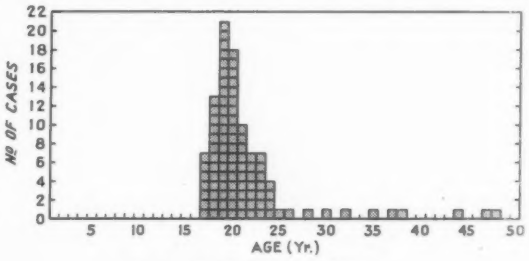

Fig. 2—Age-distribution of cases.

In the 30 cases diagnosed outside the hospital, the ages ranged between 15 and 54. At first there was a suggestion that these outside cases were confined to the immediate environs of the hospital; but in March and April isolated cases were diagnosed from widely scattered areas of the city and its suburbs. Despite careful watch, we never encountered a child with the disease. Several of the nurses affected contracted the disease while nursing in the children's wards of the hospital (which admit children up to 12 years of age), but children of all ages apparently remained immune. This suggests that, unlike poliomyelitis, the changes at puberty render the individual susceptible, since cases occurred in adolescents and the incidence among teenagers was high.

Clinical Picture

Considerable variation was seen in the severity of the disease, the course of the illness, the recovery-rate, and sequelæ. In certain cases symptoms and signs were very slight, and recovery was rapid; in others the illness proved extremely debilitating and protracted, with residual signs or relapses three years after the onset.

Four distinct phases were observed—namely: (*a*) prodromal, (*b*) acute, (*c*) convalescent, (*d*) chronic.

Prodromal Phase

Patients presented typically with severe occipital headache up to fourteen days preceding the onset of the acute phase. The headache

was usually accompanied by extreme lassitude, sore throat, painful or burning eyes, coryza, nausea or vomiting, and severe backache; there was occasional diarrhœa. Hyperhidrosis of the extremities was very common. Usually the patient ascribed these symptoms to a respiratory-tract infection or influenza.

Acute Phase

This was ushered in, often dramatically, by sudden weakness and a feeling of heaviness in one or more extremities, predominantly on the left side. Stiffness of the neck muscles was associated with severe occipital headache, weakness of the back and abdominal muscles, and inability to sit up unaided. Paræsthesiæ or severe pain in the affected limb were common. In most cases the patient stated that " the limb does not belong to me ", or that she " had to talk to it " in order to initiate movement.

Paralysis was present in at least one extremity; exercise or attempts to exercise, increased the paralysis. Muscle cramps were common, and occasionally there were bladder symptoms—either of dysuria or retention.

Convalescent Phase

This phase was extremely variable; in a minority it was short, but in the majority symptoms persisted for one to three months, and tended to recur on return to duty. The relapse was identical with the initial onset; and in those so afflicted the disablement continued for six to nine months, and then either resolved or persisted as a lack of endurance in the muscles originally involved.

Chronic Phase

This involves 11 patients who, after three years, are still disabled. Of these, 10 have been invalided out of the nursing service, and 1, a senior sister, is on duty with a permanent foot-drop. The disabilities of the remaining 10 consist of: almost complete paralysis of one leg (2); partial paralysis of an arm (2); weakness in both legs and one or other arm (3); severe back weakness, associated with paralysis of a leg (2); and generalised weakness of an arm, the back, and one leg (1). 3 are married, and have since given birth to normal children. In all cases the degree of paralysis has varied from time to time and been aggravated by pregnancy or by increased activity. In none is there any appreciable muscle wasting.

PHYSICAL FINDINGS

A low-grade fever, not above 100°F, and not lasting more than forty-eight hours, was present in the majority. The temperatures were taken only at 8 A.M. and 2 P.M.; and commonly a disproportionate tachycardia was present which may have been due to an undetected pyrexia. A minority were acutely ill, and in all cases evidence of systemic disturbance was present. Neck stiffness, but not true neck rigidity, was evident; in a few cases shotty glands in the posterior triangle were palpated, but this finding was of doubtful significance. Reversal of the normal sleep pattern was common.

Cranial Nerves

A few patients complained of diplopia, and in these there was evidence of transitory ocular paresis. Initially nystagmus was common; and in 3 cases slight facial muscular weakness presented, which may have been due to involvement either of the muscle itself or of its nerve-supply. In these patients the weakness was associated with patchy diminution of facial sensation. 1 patient had difficulty in swallowing, and in some there was absence of the " gag " reflex or exaggeration of the jaw-jerk.

Motor System

The most striking changes were found in the muscles. Individual muscles were extremely painful and tender on palpation or movement, and in the early stages were of a definite rubbery consistence. Proximal or distal muscle-groups, or the whole limb, were affected. The majority presented initially with flaccid paresis, which became hypertonic within forty-eight hours. A few were hypertonic from the onset, whilst others remained flaccid. In some, the paralysis spread to involve further muscle-groups or another limb. In the hypertonic phase, despite severe weakness, the muscles retained some contractile power, but this was of a bizarre type. Great difficulty was experienced in initiating movement; and when contraction took place it was slow and clonic-like, both agonists and antagonists appearing to contract simultaneously. Further, when these muscles were tested against resistance, they contracted in a curious interrupted or cog-like fashion. This was most evident in the long muscle of the extremities.

Pain was often extreme in the affected areas, even at rest, and was aggravated by movement. In many cases the patient could not bear the weight of the bedclothes. Muscle spasm, with attacks of cramp, caused much distress, and twitching or fasciculation was also observed. Since exercise definitely aggravated weakness and pain, physiotherapy in the initial stages was contraindicated.

Weakness of the back and abdominal muscles, with severe pain at the base of the spine and inability to sit up unaided from the supine position, was present in every case, and became an important diagnostic feature.

Reflexes

These were variable. In a small proportion of cases the reflexes subserving the affected parts were absent, but generally the reflexes were depressed in the flaccid phase. As the muscles became hypertonic the reflexes returned to normal or, more commonly, became exaggerated. True extensor plantar responses were never obtained, although some were equivocal.

Sensation

Patchy areas of diminished sensation to pain, temperature, and touch, not conforming to any anatomical pattern, were found over the affected muscle-groups but also in other areas—particularly the upper aspect of the shoulder, over the supraspinatus muscle. In the majority of cases vibration and position sense was impaired in the early stages.

Sphincters

10 patients had retention of urine with overflow incontinence, and a tendency to polyuria; 1 such case resembled diabetes insipidus.

Progress of the Illness

Severe intermittent headache persisted, in many cases for up to four or five weeks, and in a few has recurred at intervals, even up to the present date. The headache remained occipital and was often associated with neck stiffness, nausea, and vomiting. A few complained of earache and deafness, and in 6 cases a dry otitis externa with a herpetic eruption on the affected eardrum was observed. Audiograms revealed a mild transient nerve deafness. Frequently, subcostal pain of the Bornholm type was encountered; and in 1 case there was associated respiratory impairment, necessitating a short period in the respirator.

The cranial-nerve symptoms usually disappeared spontaneously, but the muscle weakness persisted for short or long periods with a number of relapses. Day-to-day variation in the severity of the paresis was noted, but no detectable wasting of the affected muscle-groups was evident. In mild cases convalescence lasted from one to four weeks, during which there were muscular aching or tiredness and occasional headaches. In the middle or intermediate group, which constituted the majority, the initial symptoms increased during the first few days. Thereafter gradual improvement took place, with return to normal in about three to four months. In the more severely afflicted, recovery has been rapid, slow, or incomplete.

TABLE I—HÆMATOLOGICAL FINDINGS

Investigation	No. of patients investigated	Result
Hb	79	Range: 11–17 g. per 100 ml.
Packed-cell volume	79	Range: 40–45%
E.S.R. (Westergren)	80	Range: 2–13 mm. in 1st hr. in 95% of patients *
White blood-cells	79	Range: 3800–10,000 per c.mm. in 95% of patients †
Differential white blood-cell count	37	In 3 patients eosinophils increased to 8%; no other abnormality
Red cell morphology	37	No abnormality

* 1 patient had an E.S.R. of 23 mm. in the 1st hour, and 3 others of 17 mm. These were the sole abnormal findings in these patients.
† 1 patient had 16,600 white blood-cells per c.mm., and 3 others 12,200, 12,500, and 11,000 per c.mm. No other abnormal findings were recorded in these patients.

In these severe cases the clonic contractions of muscle-groups, when tested against resistance, spread to involve other muscle-groups, and even the whole body, this resulting in uncontrollable shaking. This was also noted during convalescence. In some cases, particularly in the latter stages of the illness, headaches were preceded by a tendency to polydipsia.

Relapses

Relapses of considerable severity continue. The relapse usually presents in the initially affected muscles, but sometimes spreads to other muscle-groups, even after an interval of many weeks. The reflexes in these cases are mildly depressed, but continue to be variable as do the subjective sensory changes.

In 6 cases which relapsed with symptoms of persistent headache, nausea, and vomiting, the C.S.F. pressure was found to be below 50 mm. H_2O.

Psychological Changes

A predominant feature in all the cases was alteration in either intellect or affect, or both. In the early stages the majority of the nurses showed euphoria, with a desire to return to duty and an attempt to dismiss their difficulties lightly. In a minority there was pronounced depression or apathy, which developed in the more tense or emotionally unstable, some of whom are now among the cases still showing serious and distressing sequelæ. Most of the nurses involved exhibited, to a varying degree, inability to concentrate, defective memory, persistent drowsiness, emotional instability, and irritability; yet, at the same time, they displayed an apparent lack of concern as to possible serious sequelæ corresponding almost to a hysterical *belle indifference*. In many of the patients personality changes were evident and were described by relatives and close friends. These changes, at times, appeared hysterical and were associated with severe emotional instability and suggestibility. Mood swings, which previously had not existed, became evident.

TABLE II—BACTERIOLOGICAL AND PARASITOLOGICAL FINDINGS

Investigation	No. of patients investigated	Result
Throat swab examined for pathogens	56	No pathogenic organisms isolated
Stool examined for pathogenic organisms	20	No pathogenic organisms isolated
Stool examined for parasites	20	No parasitic infestation recorded

As some of the patients had a stable family background and early environment, and had never shown any tendency towards psychoneurosis, we contend that this syndrome, per se, induces emotional changes which may subsequently be regarded as hysterical in the stable individual, or aggravate a pre-existing psychoneurotic trend. On formal testing, concentration and attention were impaired with some interference in apperceptive abilities—although this interference may have been due to impaired volition.

Special Investigations

Clinical Pathological Findings

Hæmatological findings (table I).—No morphological abnormalities were found. 4 patients had a slightly increased erythrocyte-sedimentation rate (E.S.R.), and 4 had mild leucocytosis.

Bacteriological and parasitological findings (table II).—No pathogenic organism was isolated from the throat or from the stools, nor were parasites found.

Chemical pathological findings (table III).—The C.S.F. was essentially normal; in 1 patient the C.S.F. contained 79 lymphocytes per c.mm., but all others had less than 4 cells per c.mm.

Virus Studies

As it was generally suspected that the infection was

TABLE III—CHEMICAL PATHOLOGICAL FINDINGS

Investigation	No. of patients examined	Results
C.S.F.		
Pressure	88	Normal
Cells	88	79 lymphocytes per c.mm. in 1 case; less than 4 cells per c.mm. in all others
Protein	88	Range 10–40 mg. per 100 ml.
Globulin (phenol precipitation)	88	No excess recorded
Chlorides (as NaCl)	88	Range 680–790 mg. per 100 ml.
Reducing sugar	88	Range 63–80 mg. per 100 ml.
Urine		
Examined for protein and reducing sugar, and spun deposit examined microscopically	89	No protein or reducing sugar detected; no abnormal microscopic findings
Liver-function tests		
Bilirubin	15	Range 0·3–0·8 mg. per 100 ml.
Alkaline phosphatase	15	Range 5–10 K.A. units
Thymol turbidity	15	Range 2–4 units
Cephalin-cholesterol flocculation	14	Neg.
$ZnSO_4$ turbidity	15	Range 1–2 units
Total protein	15	Range 6·4–7·2 g. per 100 ml.
Serum-albumin	15	Range 3·6–4·5 g. per 100 ml.
Serum-globulin	15	Range 2·1–2·3 g. per 100 ml.
Serum paper-electrophoresis	15	No abnormality of any fraction recorded
Blood-electrolytes		
Serum-Na	10	Range 133–140 mEq. per l.
Serum-K	10	Range 4–5 mEq. per l.
Serum-Cl	10	Range 109–112 mEq. per l.
Serum-Ca	10	Range 5–10 mEq. per l. (10–11·7 mg. per 100 ml.)
Serum-P	10	Range 3·7–4·3 mg. per 100 ml.
CO_2-combining power	10	Range 23–28 mEq. per l.
Plasma-choline-esterase activity	15	Range 80–100%; pH 0·8–1·1
Urinary creatinine excretion	15	Range 0·9–1·3 g. per 24 hr.
Urinary creatine excretion	15	Range 0–0·07 g. per 24 hr.
Urinary heavy-metal excretion (As, Hg, Bi, Pb, Ag)	15	No heavy metals detected in 24-hr. urine specimens

caused by a virus, and as in similar outbreaks elsewhere attempts to isolate the virus had proved unsuccessful, a full-scale effort to isolate a virus in the Durban cases was undertaken by the Poliomyelitis Research Foundation Laboratories, under the direction of Dr. James Gear.

At first, material from patients was flown direct to the laboratories in Johannesburg. The study of this material, which gave negative results, is still being continued. Up to the present, attempts have been made to isolate the virus by a comprehensive series of tests. When it became apparent that these studies failed to reveal the cause of the condition, a unit of the laboratories was established in Durban, to allow examination of fresh specimens. In Durban, suspensions prepared from throat washings, blood, and fæces were inoculated into tissue-culture tubes of monkey-kidney tissue, chick-embryo tissue, human tissues, and also chick embryo. Specimens of muscle obtained at biopsy were similarly treated. Many passages were made in each case, but so far no virus has been grown.

Toxicological Investigations

Twenty-four-hour specimens of urine were examined by Dr. B. W. Marloth, of the Government Chemical Laboratories, Johannesburg, for the presence of a toxic substance. Urinary extracts prepared by him were handed to Dr. B. de Meillon, of the South African Institute for Medical Research, who tested these for the presence of a substance toxic to the larvæ of *Ædes ægypti*. In some urines, positive results were obtained; and a non-nitrogenous acidic body, which could not be identified, was found to be the cause of the toxicity to the larvæ. Control urines, allowed to stand for fourteen days, produced a similar, though less toxic, reaction. An even stronger reaction was obtained from purified extracts of test urines which had been allowed to stand for two and a half months.

Using a method described by Howard (1947) for the detection of small amounts of benzenehexachloride (B.H.C.)—which method is also applicable to the detection of small amounts of dicophane (D.D.T.)—samples of urine were tested for hydrolysable organically bound chlorine. The results failed to show the presence of a halogenated hydrocarbon, and therefore both these insecticides were excluded. It was likewise not possible to establish the presence in these urines of the insecticidal substance ' Parathione ' or its breakdown product, paranitrophenol. Dr. S. M. Joubert, of the Natal Provincial Central Pathological Laboratory, examined twelve urine specimens for the presence of arsenic, bismuth, copper, lead, and mercury, with negative results.

Muscle Physiology

Dr. B. V. Schulze, of the department of physical medicine, carried out investigations on 25% of the nurses.

Controls

Normal controls were chosen from the same age and sex groups, and the same muscles were investigated. Additional controls comprised patients with poliomyelitis or traumatic severance of a motor nerve, or anæsthetised, curarised patients.

Summary of Findings

No chronaxie figure over 0·25 millisecond was obtained, and therefore in all cases the peripheral nerve was excitable and excited the muscle.

In only 1 instance was the excitability of the peripheral nerve decreased. In this particular case recovery to normal chronaxie attended clinical recovery.

In the milder cases there appeared to be no functional disability of the peripheral motor nerve or muscle, or myoneural junction, and the results suggest that the paralysis is either at the synapses or central to them, in the central nervous system.

In the more severe cases there appeared to be some decrease in peripheral nervous excitability. This might be due to impairment after central damage, or to primary peripheral involvement.

Even in these severe cases, the muscle or myoneural junction did not appear to be involved.

Histopathological Investigations

Three muscle biopsies were done, the material being removed from the belly of the tibialis anterior muscle. These cases were in the convalescent phase, and the site was chosen because in the electrical testing this muscle had exhibited a decrease in excitability. No abnormality was found.

Treatment

In the acute phase complete bed rest is essential, since any form of activity tends to evoke painful cramps in the affected muscle-groups. Moreover, in our most serious relapse cases, most of the nurses admit to having been active during the acute phase.

Heat and gentle local massage may relieve spasm, but, in general, external stimulus precipitates acute cramps and pains; antispasmodic drugs have no effect.

In the convalescent phase treatment is complicated by the patients' fear that movement or activity may cause relapse.

Corrective operative procedures may be necessary; but surgery has so far been postponed in the hope of ultimate spontaneous recovery.

Discussion

The Addington Hospital outbreak resembled epidemics in other parts of the world. The significant characteristics were the closed nature of the epidemic; its onset, the acute infection occurring concurrently with poliomyelitis; the disseminated lesions; the tendency to relapse; the permanent sequelæ; and the psychiatric concomitants. As in similar outbreaks this condition was largely confined to the nursing staff in a closed institution, although patients were later seen in the outside community, many of whom had not had any known contact with the hospital nursing staff. These cases were, however, sporadic and widespread, whereas the major outbreak was localised and explosive.

Initially, a toxic cause was considered, and this promoted the intensive toxicological studies and epidemiological investigations. In favour of an intoxication was the absence of spread to other hospital personnel and the normal E.S.R., blood-chemistry, and C.S.F. findings. Added to this was the known increase in the use of insecticides during a poliomyelitis epidemic, and the finding of hypertonic and fasciculating muscles which suggested a possible toxic substance affecting the neuromuscular junction. The toxicological investigations, however, failed to incriminate any product which might have been inadvertently ingested or inhaled. Points in favour of an infective origin were the mild pyrexia, the signs of upper-respiratory infection, the apparent case-to-case spread, and the generalised systemic symptoms and signs. It was also significant that the outbreak, as in the case of

the Royal Free Hospital (Medical Staff of the Royal Free Group of Hospitals 1957) followed a hot dry summer, and was associated with a poliomyelitis epidemic. The above facts would lend support to the theory that the condition is infective, closely related to poliomyelitis, and of virus origin.

It has been suggested that the disorder is an encephalomyelitis, but the absence of a true cellular reaction, indicated by the normal C.S.F., would tend to discount this. The blood-pictures in the Addington outbreak differed from those recorded in the Royal Free Hospital, since in the Addington series no morphological abnormalities were found. On the whole, as in all other published accounts, there is a minimum of clinical or pathological data to aid precise diagnosis. In the absence of any significant pathological change in the C.S.F. at any stage of the illness, we would postulate an encephalomyelopathy rather than an encephalomyelitis. In this respect, comparison with disseminated sclerosis is of interest in view of the normal C.S.F. findings in the early stages of this disease. Siggurdsson and Gudmundsson (1956) report that the number of cells in the C.S.F. is within the normal range in cases examined after six years. This has been our experience after three years; but, in those cases examined because of persistent occipital headaches, the C.S.F. pressure has been 40 mm. H_2O or less. Whilst the site of the lesion remains obscure, the slowness of initiation of voluntary movements, the defects in cerebration, and impairment of memory, particularly for recent events, would indicate central involvement. Similarly, the variable emotional reactions, with lability and instability, the presence of euphoria or depression, and the hysteria-like features, seem to incriminate either the temporal lobe, the hypothalamus, or even the reticular formation of the midbrain. In this respect the often-altered sleep pattern, and polydipsia with polyuria, sometimes preceding the occipital headaches, are worthy of note. Further the clinical signs suggest involvement of the posterior columns of the cord and possibly the pyramidal tracts, in view of the hypertonicity, although in the Addington cases no frank extensor plantar responses were elicited. Certain cranial and peripheral nerves were found to be involved, while the rubbery consistence of the muscles, and their tenderness and spasm, indicate myalgia. The lesions therefore appear to be disseminated; and this accords with the necropsy findings of Crowley et al. (1957).

It is difficult to correlate the obvious muscle involvement with the absence of histological change or wasting, despite long-continued muscle weakness and inactivity. In view of the return to full muscle power after rest, the absence of histological changes, and the negative electrical investigations, it appears unlikely that permanent neuronal damage has occurred. This suggests that the histological change may be a disseminated demyelination with surrounding œdema, anoxia, and perivascular cellular infiltration.

A disturbing feature in our cases has been the psychiatric changes. These have been fully described by Pellow (1951) in Adelaide, and White and Burtch (1954) in New York. They have occurred both in patients with a psychoneurotic diathesis and in stable, emotionally mature individuals. Some of these have displayed features remarkably akin to hysteria.

Despite various hypotheses, this disease remains a mystery.

Summary

An explosive epidemic illness in nurses at a Durban hospital is described.

The syndrome, which superficially resembled poliomyelitis (of which there was a recognised epidemic at the time), was similar to that in outbreaks recorded in other parts of the world.

The illness is characterised by diffuse involvement of the central nervous system, associated with myalgia, and the term epidemic myalgic encephalomyelopathy is suggested.

The ætiology remains obscure, but the evidence suggests that the cause is infective.

The illness showed a predilection for a closed institutional community, but it also occurred sporadically amongst the general population. Children below the age of puberty seem to be immune.

We should like to thank the following who have contributed towards this paper: the medical superintendents of Addington and Wentworth Hospitals; Dr. James Gear, director of the Poliomyelitis Research Foundation, and his team, who undertook the virus studies; Dr. B. W. Marloth and Dr. Botha de Meillon, for their toxicological investigations; Dr. S. M. Joubert, Natal Provincial pathologist; Dr. G. D. English, the medical officer of health for Durban; Dr. A. L. Ferguson, deputy director of the Department of Health for South Africa, and Dr. E. Fallois, also of this department; Dr. M. Adnams, who was immediately responsible for the initial care of the cases and the recording of the follow-up; the investigating committee, which included Dr. M. Casson, Dr. B. V. Schulze, Dr. S. Alexander, and Mr. C. J. Kaplan, who first drew our attention to the similarity of this condition to outbreaks elsewhere.

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BENIGN MYALGIC ENCEPHALOMYELITIS
AN OUTBREAK IN A NURSES' SCHOOL IN ATHENS

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IN June, 1958, an obscure neurological illness, involving 27 cases, spread epidemically in the Queen Frederica School for Midwives, which is attached to the Alexandra Maternity Hospital. The major part of this teaching hospital is occupied by the University Department of Obstetrics and Gynæcology, and the rest of it by the University Department of Clinical Therapeutics (a medical department) to which the patients were admitted. 25 of the patients were graduates or student midwives of the above-mentioned school; of the remaining 2, 1 was a female servant of the outpatient medical clinic, and the other a nurse of a neighbouring hospital who visited the laboratory of our hospital almost daily while on duty. No patient or doctor of the Department of Obstetrics, where the nurses had been working during the prodromal stage of this illness, was affected. None of the

staff or the patients of the Medical Department, where the affected nurses were isolated, was affected; and none of the nurses of the Medical Department, who live in separate quarters, fell ill. The age of the patients ranged from 18 to 26 years with 2 exceptions (33 and 43 years).

The disease had many features in common with those in several other outbreaks recorded in the past decade (Sigurdsson et al. 1950, Acheson 1954, Macrae and Galpine 1954, White and Burtch 1954, Alexander 1956, Medical Staff of the Royal Free Hospital 1957, Shelokov et al. 1957, &c.). These outbreaks have been regarded as representing a new entity—benign myalgic encephalomyelitis (*Lancet* 1956) or epidemic neuromyasthenia (Shelokov et al. 1957). On the Continent such an epidemic was described in Denmark by Fog (1953). Three outbreaks in Switzerland between 1937 and 1939, then thought to be of atypical poliomyelitis, were probably, according to Gsell (1958), of a similar nature.

The Outbreak

The first case was admitted on May 25 and was diagnosed as polyradiculitis of unknown origin, although the clinical features did not fit into any known clinical pattern. In the following three weeks several midwives complained of muscular aches and considerable fatigue; these complaints were not given serious consideration, but later some of the patients reported severe muscular aches and paresis. At that time (about June 20) it became evident that the patients had many symptoms in common, constituting a recognisable epidemic clinical picture; all the patients were therefore isolated in the Therapeutic Department. Closing of the hospital was not considered necessary as the attack-rate seemed to be abating: in fact only 3 new cases occurred between June 20 and 30, and these were the last observed.

At the same period 20–30 additional student midwives and 3 nurses of the Medical Department complained of slight and brief muscular aches; these were possibly abortive cases of the disease but may have been due to simple fatigue which was viewed with suspicion because of the prevalent epidemic.

CLINICAL PICTURE

The prodromal phase of the disease was characterised in the majority of our patients by slight or severe muscular pains of two or three weeks' duration accompanied by unsteady gait, numbness of the lower limbs, considerable weakness, and malaise. A minority had low-grade fever, headache, loss of appetite, and malaise, which lasted for four or five days. When the disease was fully developed, the preexisting muscular pains and weakness were more severe or, where these had not previously been present, there was sudden onset of myalgia. In 2 cases the main disease was ushered in by high fever (102–104°F), headache, and stiff neck without other meningeal signs.

The important symptoms are shown in table I. Muscular pains, noted by all patients, were located most often in the lower extremity, less frequently in the upper extremity, the back, and the neck, and infrequently in the thorax and abdomen. They were either continuous or came on in paroxysms during which the involved muscles were contracted; in the latter case there were long intervals during which the patients had only slight pains and could even walk. There were also subjective sensory changes in the involved limbs (numbness, pins-and-needles, tingling, sudden changes of temperature), headache, loss of appetite, giddiness, and occasionally diplopia. Some of the patients had low-grade pyrexia with wide variation between morning and evening temperatures—a feature observed also by Shelokov et al. (1957). Gastrointestinal disturbances were virtually absent, except in 1 case where they dominated the clinical picture (severe epigastralgia, nausea, and vomiting). Photophobia was a transient feature in 4 patients, double vision in 2, and blurring of vision in 2. Commonly the intensity and character of the symptoms fluctuated, even during a single day; this was one of the most important characteristics of the disease.

TABLE I—MAIN SYMPTOMS

Symptoms	Cases	
	No.	%
Muscle pains	27	100
Subjective sensory disturbances	20	74
Headache	18	67
Muscular contractions	14	52
Pyrexia	12	44
Loss of appetite	10	37
Neck stiffness	4	15
Photophobia	4	15
Double vision	2	7
Severe gastrointestinal symptoms	1	4

TABLE II—SIGNS

Signs	Cases	
	No.	%
Tenderness at periosteum, tendon sheaths	20	74
Abnormal tendon-reflexes	17	63
Objective sensory disturbances	15	55
Equivocal plantar response	13	48
Pareses	12	44
Lasègue?	7	26
Abnormal abdominal reflexes	6	22
Joint effusion?	3	11
Nystagmus	3	11
Œdema of hand	3	11

The important signs are shown in table II. Most of the patients exhibited pronounced tenderness at the periosteum, tendon sheaths, and periarticular tissues, sometimes accompanied by swelling and hydrarthrosis; such an involvement does not seem to have been described before. On the other hand, involvement of the reticuloendothelial system was not observed, although signs of this were carefully sought in view of their prominence in the Royal Free Hospital epidemic.

In the paretic cases muscle weakness was hardly ever severe and was accompanied by brisk tendon-reflexes or, less often, by diminished tendon-reflexes, in a few by diminished or absent abdominal reflexes, and frequently by equivocal plantar responses (never extensor). The pareses and pains were sometimes limited to one or other half of the body. In no instance was there atrophy of muscles. The pareses could not easily be assessed because the patients were reluctant to move the tender limbs, but they were clearly noticed between painful periods. At the height of the paresis, contraction against resistance was either impossible or the muscle yielded tremulously. Sometimes moderate hypotonia was noted. In the affected limbs superficial sensibility was impaired; there was usually diminished perception of touch and pain, but sometimes hyperalgesia was prominent. In 1 patient light touch of the severely hyperæsthesic skin of the tibia produced a painful sensation at the outer surface of the femur. In a few patients extension of the lower limb produced a painful sensation along the sciatic nerve; in view of the intense muscular pains it is doubtful whether this was a genuine Lasègue's sign.

Signs of cranial-nerve involvement, except those mentioned above and disturbances of micturition, were not

observed. Nystagmus was occasionally noted in 3 patients; the fundi and visual fields were not affected.

2 patients had painful swelling of the hand; another 2 painful swelling of the foot, especially after walking. Objective local temperature changes were confirmed in some of the patients who complained of such feelings.

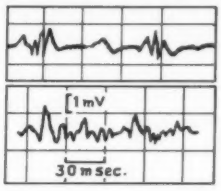
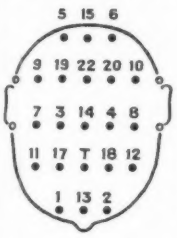


Fig. 1—Electromyograms of tibialis anterior muscles, taken at the maximum voluntary effort of the muscle, showing: above, decrease in number and grouping of motor-units; below, normal pattern.

Psychic disturbances were prominent throughout the disease. Most of our patients showed emotional lability with resultant behaviour changes: sometimes the patients were morose, pessimistic, and quarrelsome, and wept uncontrollably; sometimes they were overoptimistic, laughing without apparent cause. These mental changes were partly influenced by the variation in intensity of the other symptoms, but sometimes they appeared independently or even inversely to other symptoms. Even frank hysterical manifestations were observed.



In 4 cases there were more serious disturbances—namely a dreamlike state without fever in 2, mental apathy and slowing of psychic activity in 1, and severe depression and anxiety in the 4th. All of these disturbances were transient and did not necessitate special treatment.

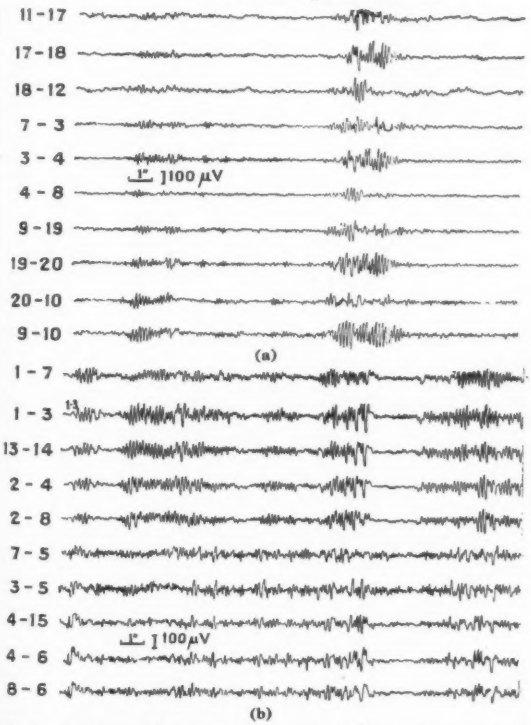


Fig. 2—Electroencephalogram of one case, showing: a, short periods of θ-rhythm; b, longer periods of θ-rhythm in all leads (replacing the dominant frequency of the record).

LABORATORY FINDINGS

Laboratory investigation did not prove helpful. Total and differential white-blood-cell counts, erythrocyte-sedimentation rate, C-reactive protein, latex fixation test, liver-function tests, &c., were all within normal limits.

The cerebrospinal fluid was examined in the 4 patients with stiff neck, and proved normal except in 1 case where a protein level of 66 mg. per 100 ml. was found.

Limited virological and bacteriological investigation is still in progress, with negative results so far.

Electromyographic studies confirmed previous reports (Ramsay and O'Sullivan 1956, Richardson 1956) of "myelopathic" lesions. In 4 of the 6 patients examined, a typical pattern consisting in reduction in the number of motor-unit potentials on volition (30–35 cycles per sec.) and grouping were observed (fig. 1). In another case single oscillations of amplitude greater than 3 mV were seen.

Electroencephalography was undertaken in 4 patients. In 3 the tracings were normal, or slightly abnormal with occasional slow-wave rhythms. In the 4th, who was the most severely affected, significant abnormalities were found (fig. 2), consisting in paroxysmal or continuous (up to one minute) slow-wave activity at the 6–7 cycles-per-sec. range and at high potentials (up to 200 μV). The abnormal waves predominated at the frontal leads; but sometimes they extended simultaneously to all leads, when θ-rhythm replaced the basic α-rhythm. This abnormality was therefore more severe than that recorded by Ramsay and O'Sullivan (1956), where slow-wave activity was of short duration and limited to the post-central leads. This patient will be followed up by repeat electroencephalography.

TABLE III—DURATION OF THE DISEASE

Duration (months)	Cases	
	No.	%
<1	16	59
1–2	8	30
2–3	2	7
3–4	1	4

DURATION AND SEQUELÆ

More than half the patients (see table III) left the wards within a month after admission and were able to resume duty after a short sick-leave, without any symptoms or neurological abnormality on follow-up examination. The more severely affected patients had repeated relapses during convalescence; and these were especially severe if they got up too soon. On walking the patients showed a peculiar limp due partly to quadriceps weakness and partly to painful sensations in the knees or soles of the feet.

1 patient, in whom the onset had been febrile, a month after leaving hospital had a febrile episode with recrudescence of weakness in her arm. Another patient still has an area of hypoalgesia at the outer aspect of the femur. In another case extension of sick-leave was advised, because of recrudescence of swelling in her hand. Thus, relapses are not uncommon, although the eventual outcome is good.

Discussion

The various outbreaks recorded under the name of benign myalgic encephalomyelitis or epidemic neuromyasthenia have many similarities but differences in details. The outbreak described here resembles those described by Fog (1953) and White and Burtch (1954).

In contradistinction to the English epidemics, involvement of the reticuloendothelial system was not observed, and the pareses were slighter and more transient; moreover no sphincter disturbances were noted and cranial-nerve involvement was rare. A unique feature in our cases was the involvement of joints and periosteum.

Although hitherto no viral or bacterial agent has been isolated, the contagiousness of the syndrome strongly suggests an infectious (probably viral) ætiology. Its predilection for females and for nurses poses interesting epidemiological questions. Only 2 of our patients were infected by case-to-case contact: this suggests that simple contact, however prolonged, does not bring about transmission. Continuous and intimate contact, coupled possibly with an infectious focus, are probably necessary —as with the graduate and student midwives, who were living and working together.

No therapeutic measure proved effective, except in providing slight palliation, which was achieved mainly with analgesics and with tranquillisers of the chlorpromazine and promazine group. Prednisone was tried in adequate dosage without any effect.

The clinical and laboratory findings suggest that the central nervous system is diffusely involved. It seems probable to us that the lesions are rather limited to the grey matter, mostly at the cord level, but also in the brain —as is indicated by the occasional signs of cranial-nerve involvement, the severe psychic changes, and the electroencephalographic findings (Daikos et al. 1958).

Summary

An outbreak of benign myalgic encephalomyelitis in a nurses' school in Athens in June, 1958, is described.

The main features of the disease were intense muscle pains, slight and transient pareses, extreme tenderness at the periosteum and periarticular tissues, mental disturbances, and objective evidence of diffuse involvement of the central nervous system.

Electroencephalographic and electromyographic findings confirm the impression of involvement of the central nervous system.

We are grateful to Prof. N. Louros, head of the University Department of Obstetrics and Gynæcology, for permission to publish these cases; and to Prof. T. Patrikios, head of the Neurology Department of the Medical School, and our chief, Prof. B. Malamos, for advice and other help.

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"... from Françoise Sagan to *West Side Story*, adolescence is the thing; the younger generation now coshes at the door. ... In one respect this self-conscious adolescence is pathetic. It depends too vehemently on never growing up, on being outside ... In other respects its 'interrogation' is well-founded. City life is street life; gangs make the prison corridors of the modern street endurable. The argument for gangs is the argument for intimacy and for personal relationships which our benevolent society of huge organisations, block-vote parties and impersonal urban areas has forgotten about."—V. S. PRITCHETT, *New Statesman*, March 28, 1959, p. 448.

EFFECT OF SMOKING ON GASTRIC SECRETION

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A CAREFULLY controlled study by Doll et al. (1958) showed that smoking can be a factor in the production and maintenance of peptic ulcer. In the ætiology of peptic ulcer two factors—acid-pepsin secretion and mucosal resistance—are of salient importance, and it is not clear which of these is predominantly affected by smoking. Studies of the effect of smoking on gastric secretion have given varied results, some investigators claiming that smoking depresses or has no effect on gastric secretion (Johnson 1929, Schnedorf and Ivy 1939, Cooper and Knight 1956), and others that gastric secretion is stimulated (Gray 1930, Crohn 1938, Rosenblum 1938, Ehrenfeld and Sturtevant 1941, Steigmann et al. 1954, Bornstein and Eichen 1954). Because of these divergent conclusions it was decided to reinvestigate the effect of smoking on gastric secretion.

Methods

The twelve subjects studied were smokers. Three had peptic ulcers, three were healthy students, and the remainder had diseases not known to affect gastric function. All were fasting, and none had smoked in the 10 hours preceding the test. All patients were studied on two occasions: (1) basal secretion was studied for the 1st hour, then the subject smoked 4–6 cigarettes in the 2nd hour, and during the 3rd hour the maximal secretory response to histamine was estimated; (2) the same subjects were studied for 2 basal hours only. The use of each subject as his own control was necessary to exclude any effect due to continued gastric suction or emotional adjustment to the passage of the tube on the gastric secretory response. The cigarettes were of different brands but all were filter-tipped.

Gastric juice was collected by a Cleland double-lumen tube, the position of which had been confirmed by screening, and continuous suction was applied with a Roberts pump. The gastric residue was aspirated initially, and continuous suction was applied for at least half an hour before measurement of basal secretion was started. All saliva was expectorated. The maximal secretory response was estimated by the response to 0·04 mg. of histamine per kg. of body-weight, the extragastric effects being abolished by 100 mg. of mepyramine maleate intramuscularly given 20 minutes previously. Specimens were collected each half-hour and were measured as regards volume, free and total acid, chloride, pH, and, in the last few, pepsin. Topfer's reagent and phenolphthalein were used in the estimation of free and total acid, and Schales and Schales' method was used for the estimation of chloride. The ^{131}I-albumin substrate method was used for the determination of pepsin (Klotz and Duvall 1957).

TABLE I—INFLUENCE OF SMOKING ON GASTRIC SECRETION: VALUES EXPRESSED AS OUTPUT PER HOUR

	Smoking experiment			Control experiment	
—	Basal hour	Smoking hour	P	Basal hour 1	Basal hour 2
Vol. (ml.) ..	80·5 ± 8·35	118·0 ± 11·0	0·01	94·7 ± 13·6	85·2 ± 13·3
Free acid (mEq.)	2·56 ± 0·58	4·39 ± 0·79	0·8	3·49 ± 0·78	3·00 ± 0·73
Total acid (mEq.)	3·71 ± 0·56	6·05 ± 1·03	0·05	4·48 ± 0·94	3·38 ± 0·78
Chloride (mEq.)..	8·25 ± 0·87	12·30 ± 1·35	0·02	9·49 ± 1·35	7·91 ± 1·32

± figure = standard error of the mean.

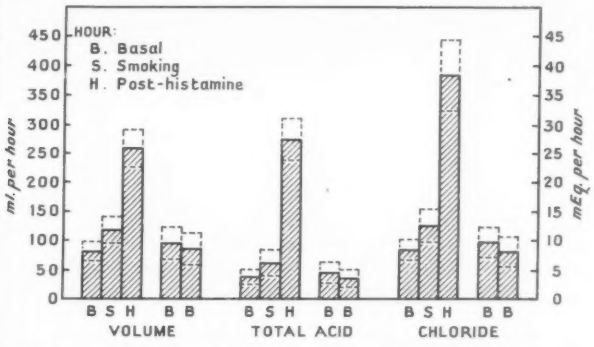

Fig. 1—Gastric secretory response (volume, acid, and chloride) during basal hour, while smoking, and after histamine. Interrupted lines = ±2 S.E. of mean.

Results

Influence of Smoking on Basal Gastric Secretion.

The results are shown in table I and fig. 1.

Table I shows that, in terms of volume, total acid, and chloride, gastric secretion is increased significantly by smoking. It is also obvious that there is a decrease in the gastric secretion during the 2nd hour of the basal experiment; for instance, of the twelve subjects only two showed an increase in volume in the 2nd hour during the control period, whereas all showed an increase while smoking. Unless this trend is considered in assessing the effect of smoking in an experiment of this design, the stimulating effect of smoking on secretion will be underestimated and an error introduced into the evaluation of the results. Consequently, the results were recalculated, the secretion in the 2nd hour being expressed as a percentage of that in the 1st basal hour and the influence of smoking assessed from the change in this percentage. The results of this analysis are shown in table II.

TABLE II—INFLUENCE OF SMOKING ON GASTRIC SECRETION: VALUES IN SECOND HOUR EXPRESSED AS PERCENTAGES OF OUTPUT IN FIRST HOUR

—	Control Experiment: 2nd basal hour (as % of 1st basal hour)	Smoking Experiment: Smoking hour (as % of basal hour)	P
Vol.	89·6 ± 7·5	156·5 ± 17·6	0·01 (t = 3·5, n = 22)
Free acid ..	68·2 ± 13·5	180·9 ± 33·5	0·01 (t = 3·1, n = 22)
Total acid ..	80·9 ± 12·8	190·3 ± 24·7	0·01 (t = 3·9, n = 22)
Chloride ..	82·6 ± 4·1	158·6 ± 21·6	0·01 (t = 3·4, n = 20)

± figure = standard error of percentage ratio.

The results show that smoking 4–6 cigarettes, under the condition of the experiment, significantly increased gastric secretion as regards volume, free acid, total acid, and chloride output. The extent of this increase is indicated by the change in free and total acid secretion, which was increased by over 100%. These findings are represented graphically in fig. 2.

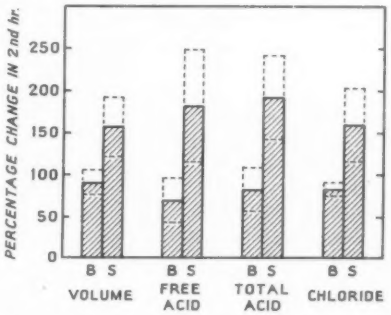

Fig. 2—Output in 2nd hour as percentage of that in 1st hour. Column B represents the change from 1st to 2nd basal hour, and column S the change from basal hour to smoking hour. Interrupted lines = ±2 S.E. of mean.

Component of Gastric Secretion Stimulated by Smoking

Possibly smoking may stimulate the parietal-cell component of the secretion or the non-parietal-cell component, or both. From volume and the free and total acid and chloride content, these two components can be calculated (Fisher and Hunt 1950). For the equations derived by these workers to be valid, there must be minimal contamination of the gastric juice with secretions from elsewhere of unknown acid and chloride content. If gastric secretion is uncontaminated, the chloride content should not drop below 125 mEq. per litre. Though every care was taken, many specimens showed chloride values lower than this, and consequently were excluded from the analysis. A study of the four subjects analysed as regards these two components of gastric secretion showed that smoking stimulated both the parietal and non-parietal cell components (fig. 3). This trend was also present in the small group in which pepsin secretion was studied; the rise in volume and acid output was accompanied by a rise in pepsin content and output.

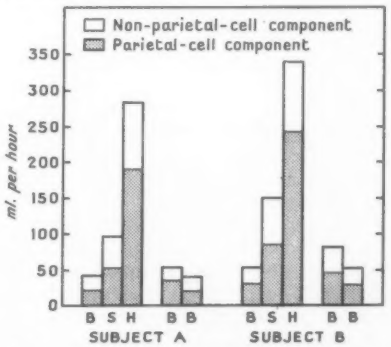

Fig. 3—Secretory response in 2 patients during basal hour, while smoking, and after histamine in terms of calculated parietal and non-parietal cell components.

Discussion

The earliest recorded experiments on the effect of smoking on gastric secretion were those of Wolff (1889) and Skaller (1909). The subject was then neglected for almost twenty years, but since then many investigators have tried to elucidate the effect of smoking on gastric secretion and the course of peptic ulceration. Little would be gained by analysing their techniques and results except to say that the variation in results appears probably to have been due to the natural variations that different patients, and even the same patient, show from time to time in basal gastric secretion, the short time during which the effect of smoking was noted, and the small number of cigarettes smoked. Also, work based on changes in the response to a test-meal is of little value unless the factor of gastric emptying is considered. Finally, as the present investigation shows, in short experiments gastric secretion diminishes with continuous suction; and this factor has been neglected. Where these sources of error have been more or less excluded, it has been shown that smoking stimulates gastric secretion (Steigmann et al. 1954). One exception to this finding are the observations of Schnedorf and Ivy (1939), who in a carefully controlled study found that smoking had no stimulating effect on gastric secretion; but they did not use each patient as his own control.

In the present study the number of cigarettes smoked was greater than would usually be smoked in one hour, though not far in excess of the number sometimes smoked by heavy smokers. Table II shows that the percentage increase in total acid attributable to smoking was 110. It has been shown that gastric secretion in patients with duodenal ulcer is at three times the normal rate (Gray 1958), and it is unlikely that stimulation of the extent demonstrated could fail to influence the course of peptic ulceration. This investigation thus supports the clinical observation of Doll et al. (1958) that smoking delays the healing of peptic ulcers.

This study shows that during smoking gastric secretion is increased, but does not indicate what component or factors are responsible. The effect of smoking on the gastrointestinal tract is usually attributed to the nicotine content of tobacco. Cigarette tobacco contains 1·5% nicotine, and the smoker of the average cigarette may receive several therapeutic doses of nicotine. Schnedorf and Ivy (1939) found that nicotine had no stimulating effect on the stomach, judged by the output from gastric pouches in dogs. This subject clearly justifies further investigation.

Summary

Smoking 4–6 cigarettes in an hour markedly stimulates gastric secretion. Both the parietal and non-parietal cell components are stimulated.

We wish to acknowledge the help given by the department of biochemistry, Knolling Institute of Medical Research, Royal North Shore Hospital, in performing the biochemical estimations involved in this investigation.

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TRIAMCINOLONE MYOPATHY

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TRIAMCINOLONE (16-α-hydroxy, Δ′, 9-α-fluorohydrocortisone) was prepared by Bernstein et al. in 1956, and reports of its use in rheumatoid arthritis (Freyberg et al. 1958, Hart et al. 1958) and disseminated lupus erythematosus (Dubois 1958) have confirmed its value as an anti-inflammatory agent. It appears to be slightly more potent than prednisolone in the therapeutic ratio of 4 to 5. Because it does not cause sodium retention it is particularly useful in cardiac disease. There is also evidence (Berntsen et al. 1957, Dubois 1958) that triamcinolone is less likely than its precursors to induce peptic ulceration. On the other hand, several side-effects have been noted which have not been seen with other steroids. Headache, drowsiness, postprandial flushing, anorexia, and progressive loss of weight have all been reported, but the most serious has been muscle weakness (Dubois 1958, Freyberg et al. 1958).

This paper describes metabolic, electromyographic, and biopsy studies on three patients with such weakness.

Case-reports

Case 1.—A man aged 56 was first seen in March, 1954, with florid polyarteritis nodosa. Since then he has been maintained on steroids—at first cortisone (150 mg. daily), later prednisolone (30 mg.), and since last April triamcinolone (24 mg.). He has remained well, though the erythrocyte-sedimentation rate (E.S.R.) has been persistently raised (20-40 mm. in first hr.). Within three weeks of starting triamcinolone, however, he complained of heaviness and weakness of the legs: he fell down on several occasions. His appetite remained good and there was no change in his weight.

On admission to hospital last July, the main findings were the cushingoid appearance, with trunk obesity and wasting of limb muscles. The flexor and extensor muscles of the hip and the quadriceps were extremely weak; but the muscles below the knee were of normal power. In the upper limbs the weakness was greatest in the abductors and adductors of the shoulder and the extensors of the elbow. Knee and ankle jerks were present though diminished and sensation was normal.

The weakness progressed so that he could not walk or even sit up in bed. When prednisolone was substituted for triamcinolone there was a steady improvement in muscle power which continued over several months.

Case 2.—A housewife aged 37 has had asthma since early childhood. This has always been hard to control, but in May, 1956, cortisone gave much relief. Since then she has had steroids in varying dosage, at times requiring up to 50 units of corticotrophin gel or 40 mg. of prednisolone daily. During this time she had been aware of slight weakness of the leg and trunk muscles, but within a week of starting triamcinolone (24 m. daily) last April she had difficulty in holding herself upright, and she fell down as many as four times in a day. Her appetite was poor, and she lost nearly a stone.

On admission in September she had general wasting of the limb muscles. Weakness was greatest in the flexors and extensors of the hips and the extensors of the knee. Reflexes were brisk and there were no sensory signs.

Within two weeks of changing from triamcinolone to prednisolone there was a definite increase in muscle power though no change in the wasting was perceptible.

Case 3.—A storekeeper aged 62 was first seen by us in 1955. He has scleroderma and a stationary neurological lesion attributed to subacute combined degeneration of the cord. Prednisolone (40 mg. daily), started in November, 1956, improved skin elasticity. In October, 1957, the dose was reduced to 7·5 mg., and he remained fairly well until changed to triamcinolone (17·5 mg. daily) last July. During the next month his arms and legs became much weaker and by September he needed two sticks for walking. But whereas previously he had been losing weight, during his four months on triamcinolone his weight was stationary and his appetite good.

He was thin, with no facial mooning or other signs of hypercortisonism. The skin over the face, chest, and extremities was tight and inelastic. There was general muscle weakness, greatest in the flexors and extensors of the hip and in the proximal muscles of the upper limb. As on previous admissions, the tendon reflexes could not be elicited and both vibration sense and postural sense were absent.

After completion of the balance studies he was maintained on prednisolone 17·5 mg. daily. By this time his condition was deteriorating and it was difficult to assess any change in muscle power.

Investigations

Metabolic Studies

Nitrogen and calcium balances were performed, together with serial estimations of serum and urinary electrolytes. The balance periods ran consecutively, except in case 1: in this patient there was a month's interval because of intercurrent illness, and as his muscle

METABOLIC DATA

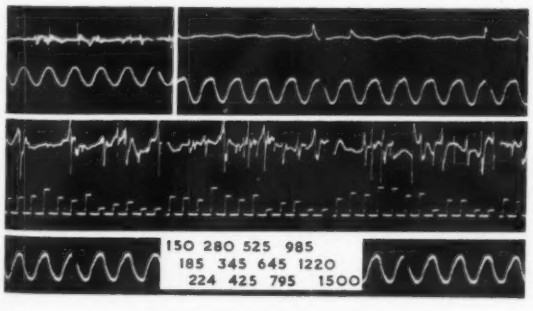
Case	Steroid (dose daily)	Days of collection	Nitrogen (g.) mean daily				Calcium (mEq.) mean daily				Electrolytes (mEq. per l.)			
			Intake	Output		Balance	Intake	Output		Balance	Serum		Urine	
				Fæces	Urine			Fæces	Urine		Na	K	Na	K
1	Triamcinolone (24 mg.), prednisolone (30 mg.)	3	8·2	1·1	11·7	−4·6	14·2	11·7	2·2	+ 0·3	140	4·3	53	22
		,,	8·2	1·2	8·8	−1·8	14·2	13·9	1·3	− 1·0	..	..	..	..
		,,	8·2	1·5	7·7	−1·0	14·2	18	1·8	− 5·6	..	..	..	..
		,,	8·2	0·9	6·2	+1·1	14·2	13·8	1·8	− 1·4	137	4·4	..	..
2	Triamcinolone (24 mg.), prednisolone (30 mg.), triamcinolone (24 mg.)	3	19·2	1·2	16·0	+2·2	46	20	19·3	+ 6·7	137	3·9	117	40
		,,	17·0	1·1	17·1	−1·2	47	24·1	18·1	+ 4·8	..	..	61	52
		,,	19·2	1·3	15·3	+2·6	46	30	15·6	+10·4	137	4·2	109	46
		,,	17·0	0·9	16·3	−0·2	47	18	21·4	+ 7·6	..	..	102	42
		,,	19·2	1·2	15·0	+3·0	46	25	25	− 4·0	140	3·8	141	58
		,,	17·0	0·9	17·0	−0·9	47	30	25·7	− 3·7	..	..	98	55
3	Triamcinolone (14 mg.), prednisolone (17·5 mg.), triamcinolone (14 mg.), prednisolone (17·5 mg.)	3	14·2	1·9	4·3	+8·0	62·3	37	2·2	+23·1	137	4·2	132	62
		,,	13·8	1·0	10·5	+2·3	62·3	53	2·0	+ 7·3	..	..	102	77
		,,	14·2	1·5	9·8	+2·9	62·3	73	1·2	+11·9	133	3·7	92	43
		,,	13·8	1·4	9·8	+2·6	62·3	54	1·1	+ 7·2	..	..	99	53
		,,	14·2	0·9	10·8	+2·5	62·3	59	1·4	+ 1·9	..	..	91	60
		,,	13·8	1·3	10·3	+2·2	62·3	80	1·0	+18·7	140	4·3	97	58
		,,	14·2	1·0	10·2	+3·0	62·3	47	1·3	+14·0	..	..	58	47
		,,	13·8	1·8	7·0	+5·0	62·3	41	1·1	+20·2	130	3·8	82	60

power had much improved we thought it unjustifiable to give triamcinolone again. The table shows that in cases 2 and 3 the nitrogen balance was similar on triamcinolone and on prednisolone. Case 2 was in positive balance when taking 120 g. protein daily and in slightly negative balance on 105 g. Case 3 was in positive balance throughout. In case 1 there was a mean daily loss of 3·2 g. nitrogen over a 6-day period on triamcinolone, compared with a gain of 0·05 g. daily over a similar period of prednisolone. The effect of the two steroids on calcium excretion appeared to be much the same, and the serum-electrolytes (including the serum-magnesium) were within the normal range throughout. The urinary sodium concentration was high, but there was no significant difference between the three periods.

Electrodiagnosis

The electrodiagnostic findings were similar in cases 1 and 2 (Dr. A. T. Richardson) and case 3 (Dr. P. Bauwens).

Intensity-duration curves derived from the weak muscles showed normal or high rheobases (5–15 mA) and in the majority brisk muscle responses to direct (100 msec.) stimulation. An exception to this was one muscle in case 3, which gave a sluggish response to direct stimulation; and both this muscle and the right tibialis anterior of the same patient showed discontinuous intensity-duration curves with threshold intensities for 1 msec. stimuli in excess of twice the rheobases (intensity at 100 msec.). All other muscles showed normal smooth-contoured intensity-duration curves with threshold intensity at 1 msec. under twice the rheobase.



Electromyograms from case 1.
Top left: spontaneous fibrillation potentials.
Top right: spontaneous positive (sawtooth) potential.
Bottom: motor-unit potentials on volition with histogram of frequency components (frequencies illustrated in cycles per sec. for one spectrum of analyser).
Calibration at 50 cycles and 100 microvolts.

Electromyograms of the muscles, while showing no or little reduction in the number of motor-unit potentials recruited on volition, revealed that the majority of these potentials were of short duration (1–4 msec.) of low amplitude (under 300 μV), and often polyphasic. All cases showed, in addition, some polyphasic motor-unit potentials of normal duration (5–10 msec.), and in case 1, some longer than normal (up to 12 msec.). Additional features were spontaneous fibrillation and positive (sawtooth potentials) in the muscles of cases 1 and 2, and high-frequency discharges in cases 1 and 3. Detailed frequency analysis of the motor-unit potentials in case 1 showed a significant increase in the high-frequency components—i.e., those above 345 cycles per sec. (see figure).

Thus in all three cases there was evidence of a primary muscle fibre lesion with additional features (i.e., fibrillation and positive potentials or abnormals intensity-duration curves) indicating the so-called neuromyopathic lesion characteristic of polymyositis.

Neostigmine Test

The neostigmine (' Prostigmin ') test was negative.

Muscle Biopsies

Prof. D. S. Russell reported on the histological appearances in cases 1 and 2.

Both biopsies show a similar picture of diffuse but uneven atrophy of the muscle fibres, the more grossly altered having the characteristic clumping and string formation of their sarcolemmal nuclei. The distribution of the atrophy does not suggest a neurogenic origin. In addition in case 1 there are scattered fibres showing degeneration and necrosis. These are pale, frequently vacuolated, and mononuclear cells (probably macrophages) are found in the interior of the fibre. There is no associated infiltration of the interstitial tissue.

Discussion

In cases 1 and 2 the weakness first appeared within 3 weeks of commencing triamcinolone, and muscle power improved rapidly when prednisolone in equivalent dosage was resumed. In case 3 the weakness could be attributed to an exacerbation of the underlying disease, but its time of onset, the similarity of the clinical picture, and the absence of other evidence of deterioration strongly suggest that it was caused by triamcinolone. Though muscles of the shoulder girdle were affected, the weakness was greatest in those of the trunk and pelvic girdle; and this proximal muscle syndrome closely resembles that seen in the muscular dystrophies and in those myopathies (presumed to be of metabolic origin) which may complicate

thyrotoxicosis and carcinoma. The myopathic origin of the weakness was supported in cases 1 and 2 by the preservation of the tendon reflexes and the absence of sensory loss. In case 3 the picture was complicated by neurological signs of long standing.

Cortisone is the main protein-catabolic hormone, and muscle wasting is a feature of Cushing's syndrome. In this condition, however, the weakness is related more to hypokalæmia and may disappear when the serum-potassium level is raised. In the present cases the serum-potassium was repeatedly found to be normal. If triamcinolone is more protein-catabolic than prednisolone, in doses which appear to be equivalent in other respects, the weakness it causes might simply be the result of muscle wasting; and there is a certain amount of indirect evidence that this is so.

In eighteen out of twenty-nine cases of disseminated lupus erythematosus treated with triamcinolone Dubois (1958) noted a steady loss of weight which he attributed to a decrease in appetite and to muscle wasting due to a probably negative nitrogen balance. Six of the eighteen developed marked muscle weakness preceded by an increased cushingoid appearance. This did not happen in any of the males, possibly because testosterone reduces protein-catabolic activity. Freyberg et al. (1958) also found that weakness with triamcinolone was associated with anorexia and loss of weight. On the other hand, Dubois found no relation between the size of the dose and the development of this syndrome. Of our three patients only one (case 2) lost weight; and she also lost appetite. In the others where was no change in weight and no appreciable increase in muscle wasting, which had been present for some time.

Dubois (1958), Hart et al. (1958), and Shelley et al. (1958) have remarked on the higher incidence of cutaneous side-effects—cushingoid appearance, hirsuties, and striæ—in patients receiving triamcinolone. In case 1 they were unchanged, in case 2 they diminished, while in case 3 they never appeared.

The results of balance studies have been rather inconclusive:

Hellman et al. (1957) found little change in nitrogen or potassium balance but Freyberg et al. (1958) using larger doses of triamcinolone (24 mg. daily, or more), with only a moderate protein intake, found that some patients had a greater nitrogen loss than during control periods.

In cases 2 and 3 we found no significant difference between triamcinolone and prednisolone in respect of protein-catabolic activity. In case 1 the two balance periods were separated by a month and it is hard to know how much importance to attach to a difference between them. Possibly there was a period of increased protein catabolism when these patients were first put on triamcinolone; but this seems unlikely since there was no change in nitrogen excretion when they were changed in hospital from prednisolone to triamcinolone. We may conclude that, in the dose ratio of 4 to 5, triamcinolone has no greater catabolic activity than prednisolone, and that the weakness therefore cannot be attributed simply to increased protein catabolism.

The electrodiagnostic investigations show in all three cases evidence of primary muscle-fibre lesion.

Though there was little or no reduction in the total number of motor-unit potentials—i.e., in the interference pattern on volition as detected electromyographically—the individual potentials were of short duration and low amplitude, and were often polyphasic. Additional evidence for a myopathic lesion is the presence of normal or high rheobases in the weak and wasted muscles. Such electrodiagnostic changes are common to all muscle-fibre lesion—e.g., muscular dystrophies (Kugelberg 1949) and polymyositis. In polymyositis, however, additional electrodiagnostic features (reviewed by Walton and Adams 1958) may be found. Whether or not these changes indicate terminal lower-motor-neurone degeneration in addition to the muscle-fibre degeneration, they are certainly characteristic of neuromyositis (polymyositis). In all our three patients two or more of these additional features were detected. Thus cases 1 and 2 showed spontaneous fibrillation and positive (sawtooth) potentials, while case 3 had abnormal intensity-duration curves. Further, besides the shift in the durations and amplitudes of the motor-unit potentials characteristic of myopathy, all three showed retention of polyphasic motor-unit potentials, of normal or longer-than-normal duration, as found in neuropathies. Finally cases 1 and 3 showed occasional bursts of high-frequency discharges (pseudomyotonic discharges) which also occur in polymyositis.

The finding of muscle damage in both muscle biopsies was of considerable interest. In case 1 no vascular changes were seen and the muscle necrosis is therefore much more likely to be due to steroid therapy than to the underlying disease. Kendall (1945) and Germuth et al. (1951) noted necrosis of skeletal muscle in laboratory animals given corticotrophin or cortisone. Ellis (1956) found that rabbits given massive does of cortisone (10 mg. per kg. body-weight for 7–25 days) developed widespread necrosis of skeletal muscle; but, when the cortisone was discontinued, the normal structure was completely restored.

The mechanism of these changes is unknown. The muscle contained more sodium and water than usual, but less potassium. As the total nitrogen content was unchanged the decrease in potassium cannot have been merely secondary to a reduction in protein content. Exactly similar histological appearances could be induced in rabbits by potassium deficiency; but in the cortisone-treated animals large doses of potassium did not prevent muscle necrosis.

Glaser and Stark (1958) by a method utilising the refractory period, found no change in muscle excitability in the cortisone-induced myopathy, whereas in the myopathy secondary to potassium deficiency muscle excitability was decreased. They concluded that changes in excitability could not be directly correlated with histological changes. In man, similar histological appearances are seen in polymyositis (Walton and Adams 1958), and it appears that muscle necrosis is not a specific lesion but represents a basic reaction of the muscle to injury.

Such massive doses of cortisone as were used experimentally are not normally given to man, and I was interested to hear from Dr. M. J. McArdle of two cases of polymyositis associated with Cushing's syndrome.

Though the effect of triamcinolone on muscle structure and function has not yet been studied, the muscle weakness in our patients seems to have been the result of a myopathy like that induced experimentally with cortisone. The different molecular structure of triamcinolone may potentiate this particular effect, and myopathy may thus occur with much smaller doses.

Summary

Three cases are described in which proximal muscle weakness followed triamcinolone therapy. Muscle biopsy was done in two of them and showed widespread muscle damage.

In all three cases there was electromyographic evidence of a primary muscle-fibre lesion. Metabolic studies showed no difference in protein-catabolic activity between triamcinolone and prednisolone in the doses used. The relation between this myopathy and that induced in rabbits with massive doses of cortisone is discussed.

I should like to thank Dr. J. G. Scadding and Dr. A. St. J. Dixon, under whose care these patients were admitted, for permission to

publish this account of them. I am indebted to Dr. A. T. Richardson for his report on the electromyograms and for his advice and encouragement, to Dr. P. Bauwens for the electromyogram in case 3, and to Prof. D. S. Russell for the histological report.

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REVERSIBLE AMYOTROPHY COMPLICATING TREATMENT WITH FLUDROCORTISONE

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THE following case, in which full and prolonged doses of fludrocortisone (9-alpha-fluorohydrocortisone) were associated with the development of steroid diabetes and muscular paralysis, is regarded as being of considerable importance. The dramatic recovery which began immediately fludrocortisone was discontinued suggests that this compound must have been a major factor in the production of the amyotrophy.

Case-record

A 49-year-old woman was admitted to the Guy's-Maudsley Neurosurgical Unit (case no. 1287) in January, 1956, complaining of headache that had been present for many years and had become severe for the past three months, during which period her sight had deteriorated to finger-counting on the right and J8 on the left. She had an expanded sella turcica, and the visual fields showed a right temporal paracentral scotoma and a left temporal hemianopia.

At operation on Jan. 27, 1956, a cystic craniopharyngioma only 0·75 cm. in diameter was found beneath the right optic nerve and probably arising from the infundibulum. All that could be seen was removed, and her vision returned almost to normal. Her sight deteriorated again, however, and the lesion was explored for the second time in October, 1956. On this occasion 0·4 ml. of Carnoy's fluid * was put into the cyst before washing it out with saline and again removing the superficial tissue. On discharge her visual acuity was almost normal. Shortly after this operation diabetes insipidus developed for a brief period.

By March, 1957, vision in the right eye was reduced to finger-counting. There was a bitemporal hemianopia with a right central scotoma. Further operation was at first refused, but in August, 1957, she was readmitted with persistent vomiting and headache. She was in a state of severe sodium depletion (121 mEq. per litre). Her blood-pressure was 85/60 mm. Hg and she was very lethargic. After two weeks on cortisone (200 mg. per day) she was very much better (blood-pressure 120/70 and serum-sodium 150 mEq. per litre). After the administration of cortisone her fluid intake had risen to 6 litres per day. The improvement in her general condition allowed a third operation to be performed on Sept. 2, 1957. The procedure was similar to that used on the last occasion, but the cyst was larger than before. A silicone rubber tube was finally placed between the interior of the cyst and the subdural space of the anterior fossa after the cavity had again been treated with Carnoy's fluid.

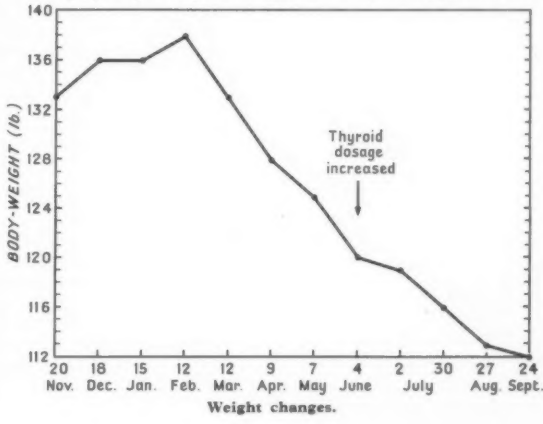
After this operation she was very euphoric. Her urinary output rose to 6·3 litres per day, and she began to vomit frequently. Her vision improved immediately and has not since deteriorated (J1 right and left); there is an almost full peripheral field in each eye, but the central fields show a bitemporal homonymous defect to small objects. A week later she became very confused and the serum-sodium was 113 mEq. per litre. The cortisone was increased to 100 mg. by mouth and 100 mg. intramuscularly per day, with 5 mg. of deoxycortone and 5 g. of sodium chloride. As she responded to treatment she ceased to vomit but her urinary output increased further and necessitated the use of vasopressin. Her symptoms were attributed to low serum-sodium associated with intracellular overhydration. She was discharged from hospital on Oct. 7, 1957, on the following therapy: cortisone 100 mg. daily; fludrocortisone 0·5 mg. daily; thyroid extract 30 mg. daily; phenobarbitone 30 mg. b.d.; vasopressin snuff 40 mg. at night. On Oct. 23 cortisone was reduced to 75 mg. daily but no other change in steroid therapy was made until her admission in September, 1958.

For five months after discharge she remained perfectly well, the blood-pressure being maintained between 150/100 and 130/80, but extreme thirst necessitated vasopressin snuff at night. This symptom improved steadily until July, 1958, but then became progressively more severe until her admission in September.

Her weight (see accompanying figure) increased until February, 1958, when it began to show a progressive fall and she had lost 26 lb. by the following September. Her appetite remained excellent throughout.

Before her discharge from hospital in October, 1957, she had been placed on a small maintenance dose of 30 mg. of thyroid extract daily because it was believed that she had become slightly subthyroid as a result of damage to the anterior pituitary gland by the tumour. In November, 1957, her serum-cholesterol was found to be 388 mg. per 100 ml. and this dose was increased to 30 mg. b.d. In June, 1958, she complained of hoarseness, and, since her serum-cholesterol was still 390 mg. per 100 ml., a further increase in the dose of thyroid extract to 60 mg. b.d. was made in spite of the continuing weight-loss at this time. Her voice recovered and the increased dose was continued until her admission in September. The increase in thyroid did not correspond to any obvious change in the pattern of her weight curve (see figure).

On July 30, 1958, she reported that, although she felt



Weight changes.

* Carnoy's fluid: absolute alcohol 6 ml., chloroform 3 ml., glacial acetic acid 1 ml.

perfectly well, she had noticed a little unsteadiness in her gait which she described as "tottery". Nothing abnormal was noted at that time but subsequently a progressive weakness of her legs became apparent and she was admitted to Guy's Hospital on Sept. 28, 1958.

Physical Examination

The patient appeared well nourished and did not look ill. Cardiovascular system: nothing abnormal apart from a blood-pressure of 140/100. Respiratory system, alimentary system, and abdomen normal. Reticulo-endothelial system normal.

Central Nervous System

Cranial nerves: normal apart from some pallor in the right disc and minor visual-field defects.

Motor system.—Marked wasting of both quadriceps. No fibrillation or fasciculation in any muscle group. Muscles of even consistence and normal temperature.

Tone: trunk and arms normal; legs hypotonic, particularly the quadriceps muscles.

Power: trunk, slight weakness of flexion and extension; arms, moderate weakness of abduction of the shoulders, slight weakness of flexion and extension of the elbows, flexion and extension of the wrists and abduction of the fingers; legs, gross weakness of flexors and extensors of the knee and hip, slight weakness of plantar-flexion and dorsiflexion of the ankles. All muscle weakness symmetrical.

Coordination normal, allowing for the weakness of her legs.

Reflexes: biceps and triceps jerks reduced bilaterally: supinator, knee, and ankle jerks absent. Plantar responses flexor.

Sensory system.—No abnormality.

Laboratory Investigations

Urine (Oct. 2) sugar ++++, albumin nil, acetone nil.

Glucose-tolerance Curves

		Glucose (mg. per 100 ml.)				
	Fasting	*½ hr.*	*1 hr.*	*1½ hr.*	*2 hr.*	*3 hr.*
Oct. 7, 1958	270	345	418	425	430	395	...
Dec. 10, 1958	100	168	No specimen	284	207	194	170
Jan. 14, 1959	95	168	262	252	178	134	110

Serum-cholesterol (Oct. 15) 460 mg. per 100 ml., (Oct. 8) 270 mg. per 100 ml.

Basal metabolic-rate (Oct. 8) +10% (upper limit of normal).

Serum-electrolytes (Sept. 30): Na 150, K 4·1, Cl 91·6, bicarbonate 27·1 mEq. per litre, urea 28 mg. per 100 ml.

Creatine excretion (Oct. 2) 1·06 g. per day; creatinine excretion 1·40 g. per day (urine volume 7600 ml.).

Total sodium excretion in 24 hours (Oct. 28) 189·1 mEq.

Total potassium excretion in 24 hours (Oct. 28) 77·0 mEq. (total urine volume 5910 ml.).

Blood-picture, electrocardiogram, empirical liver tests, alkaline phosphatase, and plasma-proteins normal.

Electromyography (Dr. J. B. Morrison)

Oct. 4: Lt and Rt quadriceps. High-amplitude potentials found of 2·5 mV, otherwise normal, but pattern reduced on full activity. No resting activity, fibrillation, or fasciculation. Rt deltoid, no abnormality. Conclusion: no evidence of myopathy detected. The high-amplitude units put the lesion either in the anterior horn cell and/or anterior nerve-root.

Jan. 15: Lt vastus lateralis. Fibrillation. Complex units of over 10 m.sec. Areas of normal and short duration units. High-amplitude potentials of 4 mV. Pattern reduced on maximal contraction. Intensity duration curves on lt vastus lateralis and lt rectus femoris show partial denervation. Conclusion: these findings confirm that the patient has a neurological lesion. The intensity duration curves, fibrillation, and reduced pattern on maximal contraction indicated lower-motor-neurone nerve degeneration. The high-amplitude potentials place the lesion in the anterior horn cell and/or anterior nerve-root, and the complex units of over 10 m.sec. and short duration units denote that recovery is ensuing.

Muscle Biopsy (Dr. J. B. Cavanagh)

Lt quadriceps (Nov. 6). Macroscopic: portion of muscle (1·2 × 0·7 cm. thick) did not show any grossly abnormal features. Microscopic: sections in transverse and longitudinal directions show that there is a general moderate reduction in size of muscle-fibre and a moderate increase in subsarcolemmal nuclei which may be largely apparent. No focal necroses and no inflammatory changes. Nerve-fibre bundles appear normal and there is no increase in fibrous or fatty tissue.

In view of the diabetes mellitus a progressive reduction in the dose of cortisone was made until it was withdrawn completely on Oct. 25. Corticotrophin gel was administered (20 units daily) for one week from Oct. 13–20 while the cortisone was being withdrawn. The fludrocortisone was reduced from 0·5 mg. to 0·4 mg. daily on Oct. 16. As soon as the cortisone had been withdrawn, however, the systolic blood-pressure fell to below 100, and a daily dose of 25 mg. was reinstituted on Oct. 29. While these measures resulted in a considerable improvement in her glycosuria, the weakness of the legs increased steadily so that by Nov. 7 they were completely paralysed apart from a flicker of movement at the ankles. The possibility that the muscular weakness might be a side-effect of fludrocortisone was considered, and on Nov. 7 this drug was discontinued, the dose of cortisone being raised to 150 mg. daily. The effect was dramatic: within three days movement began to return and this has increased steadily so that the patient can now walk without support (Jan. 10). Cortisone was rapidly reduced and her present dose is 50 mg. daily. On this regimen the glycosuria and blood-sugars improved, as shown by the glucose-tolerance curves in December and January.

The polydipsia improved steadily as the glycosuria was controlled and is now almost normal. The only other change was the introduction of a weekly injection of 19-nortestosterone phenyl propionate (25 mg.) on Oct. 25. It is not considered that this could have had any effect upon the course of her muscular weakness.

Discussion

In searching for a cause to explain the muscular weakness, various factors were considered. Myopathy can follow excessive potassium loss, and in view of the long-continued administration of a strong mineralocorticoid this seemed to provide a possible explanation. The serum-potassium and electrocardiogram were both normal, however, which appeared to exclude this hypothesis. Thyrotoxic myopathy also seemed to be ruled out by the normal basal metabolic-rate and by the absence of clinical evidence of thyrotoxicosis. The possibility that the amyotrophy might be the result of the steroid diabetes was considered. Diabetic amyotrophy has been fully described by Garland (1955) and may occur early in the disease. In Garland's patients the electromyograph gave varying results but in some the lesion did, as here, appear to lie in the region of the anterior horn cells. While most of his cases were considerably older than our patient, the youngest was 47. Furthermore, the paralysis was reversible and improvement did not always begin immediately the blood-sugar was controlled. In our patient, however, rapid deterioration continued during the first month in hospital in spite of considerable improvement in the glycosuria, and so other possible ætiological factors had to be considered.

At a meeting of the Heberden Society (*Lancet* 1958) it was reported that triamcinolone had caused excessive loss of muscle-tissue giving rise to the clinical appearance of a myopathy. As triamcinolone (9-alpha-fluoro-16-hydroxy-prednisolone) resembles fludrocortisone in possessing a fluorine atom in the 9-alpha position in the steroid nucleus, it occurred to us that fludrocortisone might be responsible for the muscular paralysis and this steroid was withdrawn on Nov. 7, 1958. Rapid and dramatic improvement was obvious within three days and seems to provide strong evidence that this steroid was playing a major part in producing the amyotrophy. As improvement began while the patient was receiving an additional 125 mg. of oral cortisone daily in place of 0·4 mg. of fludrocortisone, there was no reduction in the dose of glucocorticoid administered at this time. Although muscular paralysis does not appear to be a direct effect of fluorine intoxication, it seems possible that the presence of a fluorine atom in the 9-alpha position in the steroid

nucleus may confer this side-effect upon the compound so formed.

Summary

Severe hypotension, necessitating the administration of large doses of fludrocortisone for a year, followed surgical treatment of a craniopharyngioma. During this period the patient developed steroid diabetes and progressive muscular paralysis, especially involving the legs.

The muscular paralysis improved dramatically on withdrawal of the fludrocortisone and progressive recovery followed.

It is suggested that, in view of the cases of muscular weakness reported with triamcinolone (9-alpha-fluoro-16-hydroxy-prednisolone), the presence of a fluorine atom in the 9-alpha position in the steroid nucleus may be responsible for this complication. It seems unlikely that the steroid diabetes was responsible.

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CARBROMAL INTOXICATION

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FROM time to time the toxic effects of carbromal are reported in medical journals (e.g., Borrie 1955, Seager and Foster 1958) and, when fatal, in the daily press (*Times* 1958). But confusional states associated with habitual self-medication with carbromal may pass unrecognised; and since carbromal preparations can be purchased without prescription (and soon may be sold in shops other than chemists'), one may expect that similar cases will continue.

Of the five cases we now describe, four had long histories of mental illness, but the other was a woman of 65 with no such previous record.

Case-reports

Case 1.—A man aged 59, formerly a taxi-driver, has been in St. Ebba's Hospital since March, 1937, because of depression with hypochondriasis and delusions. He is solitary and withdrawn, but his intellect is well preserved. He has had several courses of electroconvulsive therapy each followed by brief improvement.

In 1943, after his nightly draught of paraldehyde was withdrawn, he started to take 'Aspro' tablets (bought when he was out on parole) surreptitiously at night. In 1949 he discovered that 'Persomnia' could be obtained without prescription, and he has since taken this drug fairly regularly, his usual dose being 4 tablets at night. Once in 1954 he was found to be abnormally drowsy with slurring of speech, and in 1957 he fell out of bed one night; both times tablets were found in his possession.

On Sept. 9, 1958, he did not wake at the usual time, and was found to be in coma. After treatment he became less deeply unconscious, and by 2.30 P.M. he was able to say "good morning". Next day he had a hazy recollection of taking about 20 persomnia tablets at 9.30 P.M. on Sept. 8. He remained confused and restless for 3 to 4 days after the coma, and was not fully continent for a further 2 days. On the 14th day treatment with sodium chloride and fluids was started.

Neurological examination (by Dr. John Foley) showed no evidence of permanent damage. Charting of the visual fields revealed some temporal restriction but no central scotoma.

Starting on Sept. 9 we made a series of biochemical estimations which are shown in the table and figure. Standard laboratory methods were used. Apart from a potassium of 5·7 mEq. per litre on the first day, the sodium, potassium, and bicarbonate values were consistently within the normal range.

During the first 10 days, the bromide fraction of the total urinary halide fluctuated between 14% and 30%, while that of the serum remained relatively constant at 20–23%. After treatment with salt and water, the urinary bromide fraction fell rapidly, the excretion of bromide in the urine was accelerated, and the serum-bromide level began to fall steadily, whereas previously it had remained remarkably constant despite the elimination of considerable amounts of bromide in the urine. During the first 2 weeks, conditions for the excretion of bromide were not optimum, and this is reflected in a rise in the serum-urea level. Throughout there was a close inverse relation between the 24-hour urine volume and the blood-urea level (see figure). 8 weeks after the last dose of carbromal 5 mEq. of bromide (0·5 g. as sodium bromide) was excreted in 24 hours. On Nov. 14 his urea-clearance was 81% of the normal average.

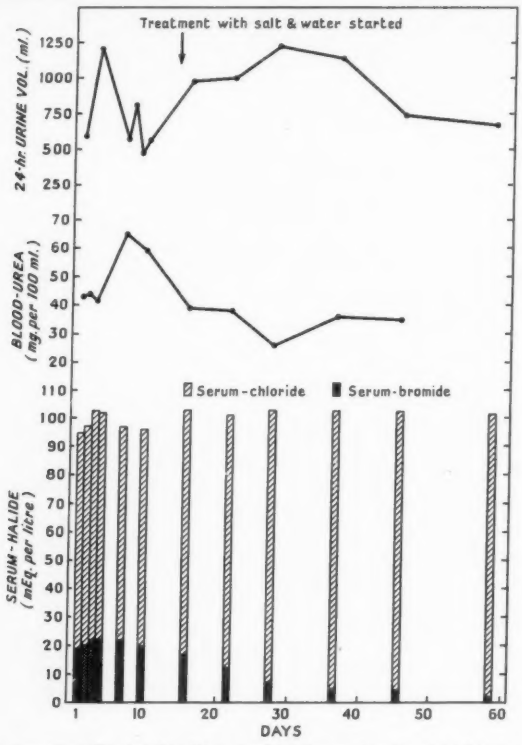
His mental state is now the same as before the coma.

Case 2.—A woman aged 65 had had a mental disorder with severe headaches and mild dysphasia for about 3 weeks; she had been taking tablets containing carbromal as well as two bottles of tablets (nature unknown) supplied by her doctor. She had had very little to eat during this period.

On admission to hospital she was confused and drowsy, sleeping most of the time, but she could be roused. She became less drowsy within 24 hours, but was still extremely restless and confused, crawling around the floor, and rambling incoherently. On examination, the eyes were held in mid-position with some weakness of both external recti, the pupils were irregular, of moderate size, and reacted sluggishly to light. Grasp reflexes could be elicited in both hands and there was some rigidity

SERUM AND URINE LEVELS AND EXCRETION OF BROMIDE, CHLORIDE, AND TOTAL HALIDE AFTER WITHDRAWAL OF PERSOMNIA IN CASE 1

—	Days														
	1	2	3	4	7	8	9	10	14	16	22	28	37	46	59
Serum:															
Halide (mEq. per litre)	95	97	103	102	97	..	..	96		103	101	103	103	103	102
Bromide (mEq. per litre)	19	20	22	22	22	..	..	20		17	12	7·5	5	4·6	2·6
Chloride (mEq. per litre)	76	77	81	80	75	..	..	76		86	89	95·5	98	98·4	99·4
Bromide as % of halide	20	21	21	22	23	..	..	21		16	12	7·3	4·8	4·4	2·5
Urea (mg. per 100 ml.	43	44	41	..	65	..	..	59		39	38	26	36	35	..
Urine:															
Volume (ml. per 24 hr.)	590	..	1210	..	570	810	480	580	Treatment started with sodium chloride and water by mouth	980	1000	1230	1140	740	680
Creatinine (g. per 24 hr.)	..	..	1·1	..	0·8	..	0·8	1·0		..	..	0·9	..	0·8	0·8
Halide (mEq. per litre)	86	..	132	..	98	105	88	105		280	254	144	216	188	226
Bromide (mEq. per litre)	26	..	20	..	19	15	12	26		24	18	10	12	9	7
Chloride (mEq. per litre)	60	..	112	..	79	90	76	79		256	236	134	204	179	219
Halide (mEq. per 24 hr.)	51	..	160	..	56	85	42	61		274	254	177	246	139	154
Bromide (mEq. per 24 hr.)	15	..	24	..	11	12	6	15		24	18	12	14	7	5
Chloride (mEq. per 24 hr.)	36	..	136	..	45	73	36	46		250	236	165	232	132	149
Bromide as % of halide	30	..	15	..	19	14	14	25		8·6	7·1	6·9	5·6	4·7	3·1



Serum-bromide, total halide, and blood-urea levels, and 24-hour urine volumes after withdrawal of persomnia in case 1.

of the extensor muscles of the forearms, but no cogwheel phenomenon. The optic discs were blurred, and there was thought to be some retrobulbar neuritis.

She was treated with large doses of nicotinic acid. Bromide intoxication was suspected; the serum-bromide was found to be 400 mg. per 100 ml. and the blood-urea 51 mg. per 100 ml. 9 days after admission her mental state was unchanged, although the pupils were then reacting more briskly. The nicotinic acid was discontinued and she was given sodium chloride (as normal saline) intravenously, by mouth, and by rectum.

A fortnight later she was still confused but was able to give her name correctly. The serum-bromide was 200 mg. per 100 ml. More intravenous saline was given, and a régime of sodium-chloride tablets and fluids ad libitum by mouth was started. She had a total of 143 g. of sodium chloride in the next 7 days, during which the blood-urea fell to 12 mg. per 100 ml. and the urea-clearance, calculated on 24 hours' output, was over 150% of the normal average. On the 2nd day the serum-bromide was 140 mg. per 100 ml., and she was still disorientated. After 7 days she had improved, her serum-bromide being 75 mg. per 100 ml.

A week later (4 weeks after admission) she was able to give an account of the events leading to her admission. Her serum-bromide was then 35 mg. per 100 ml., and 10 days later it was less than 25 mg. per 100 ml.

During convalescence (on different days) the urea-clearance was found to be 60 and 62% of the normal average, the blood-urea being 34 and 30 mg. per 100 ml. respectively. An early-morning specimen of urine was normal. 24-hour excretion tests, with and without sodium or potassium bromide, showed no tendency to bromide retention nor interference by bromide with the excretion of urea, bases, halides, and phosphates. Probably bromide retention can only be demonstrated by tests involving prolonged administration of bromides.

She was well on discharge, after 4 months in hospital.

Case 3.—A man aged 52, previously a successful business executive, had an "addictive" personality, and a history of several mental breakdowns. When seen he could not face the exacting requirements and responsibilities of his job, he lacked initiative and confidence, his concentration and memory were poor, and he had occasional dysphasia. He was drowsy yet sleeping badly, confused, depressed, emotionally labile, hopelessly pessimistic about his future, and sexually impotent. There was facial weakness, and circumoral tremor. In due course he admitted having taken persomnia habitually to help him to sleep, and when he had a hangover in the daytime he took methylphenidate hydrochloride ('Ritalin') to rouse himself. Soon a vicious circle was established; he took more and more persomnia to procure sleep, and more and more ritalin to keep awake. Abstention from both drugs produced withdrawal symptoms in the form of severe depression and aggravation of his confusion and emotional lability. This necessitated his admission to hospital, where he made an eventual but slow recovery. The blood-urea was 40 mg. per 100 ml.; the serum-bromide was not estimated.

Case 4.—A male pharmacist, aged 43, had been taking carbromal ('Adalin' tablets) for about 10 years. He had become dependent on them and was taking 7 or 8 tablets daily. He did not feel drowsy on this dosage, and he was sleeping poorly. In August, 1957, he attempted suicide, by taking about 80 tablets of adalin. He was admitted to hospital in coma, but improved sufficiently the same day to name the drug he had taken; the next day he relapsed into coma, and was treated for a time in a respirator. This was followed by a short confusional period.

Case 5.—A married woman, aged 44, was an alcoholic. For several years she had taken either paraldehyde or persomnia when abstaining from alcohol. At one time she took about 10 tablets of persomnia daily—half of them during the day—claiming that she could not manage without them or some other sedative. She noticed a loss of efficiency, felt weak and unsteady on her feet, and fainted on several occasions when out of doors. Since admission to hospital she has twice returned from "town parole" in a somnolent state, and once 86 persomnia tablets were found in her possession. The serum-bromide level was 35 mg. per 100 ml. a month after she was last known to have taken persomnia.

Discussion

Cases of carbromal intoxication similar to ours have been described by Stroh (1955), by Seager and Foster (1958) and in the Continental literature. Magnussen (1947) reported 35 cases, of which 2 were fatal and 2 were addicted to carbromal. He quotes also two cases of chronic carbromal intoxication, with serum-bromide levels of 245 and 139 mg. per 100 ml. respectively. Cases with similar features have been described by Stöhr (1951), who quotes also cases described by Freund (1915), Sattler (1923), and Herzberg (1927).

In general, the patients became stuporose, giddy, ataxic, and less efficient. Irritability and emotional lability were common, also dysarthria, memory disturbances, tremor, and fainting attacks. Some were euphoric, but more commonly they were apathetic and withdrawn, and often depressed. Many were impotent and suicidal attempts were made. Neurologically they showed brisk reflexes, circumoral tremors, facial paresis, inequality of the pupils, nystagmus, pale optic discs, and scotomata, both peripheral and central. Only the scotomata persisted after withdrawal of the drug. Withdrawal of the drug often caused aggravation of the preceding symptoms.

Stöhr likened the neurological changes to those of barbiturate intoxication; the mental symptoms differ from those of alcohol and barbiturate intoxications in that hallucinations are rare, and the psychiatric state is very similar to that of classical bromism.

In one of Sattler's (1923) cases the serum-bromide level was only 30 mg. per 100 ml., although the effects produced would

have been consistent with a serum-bromide of about 300 mg. per 100 ml. We have not been able to confirm this observation; in case 2 a bromide level of 140 mg. per 100 ml. was accompanied by considerable confusion; at 75 mg. per 100 ml. the patient's mind was much clearer, while at 35 mg. per 100 ml. she was lucid.

In our first patient the confusional state before coma may have been masked by his solitary and withdrawn habits; after he recovered from coma his mental state was unchanged. In the second the confusional state was more severe than in any previously reported case we know of, and this is reflected by the very high serum bromide level.

In both cases 1 and 2, while the serum-bromide was high there was slight impairment of renal function, as indicated by the raised blood-urea level. When extra salt and fluids were given, there was diuresis and a fall in blood-urea, and, in case 2, an increase in renal excretion with the elimination of 20–30 g. of halide daily, although the urea-clearance was later found to be below the accepted normal range.

Stöhr (1951) claimed that carbromal was a habit-forming drug, although to a lesser extent than the barbiturates. Cases 3, 4, and 5 in our series, were each dependent on the drug at some time. In case 3 an interesting feature was the aggravation of the mental disorder which followed withdrawal of the drug; this was noted also by Magnussen (1947).

At present carbromal (diethylbromacetyl carbamide) and bromvaletone (dimethybrompropyl carbamide) are the most commonly encountered bromureide preparations in this country. In addition to tablets of carbromal *B.P.C.* and bromvaletone *B.P.C.* (1949), the following proprietary sedative or sleeping tablets contain one or both drugs (*Extra Pharmacopœia* 1958):

Adalin, Bromural, Carbrital, Carbromal compound tablets, Dormiprin, Dormupax, Melosan, Noctynol, Persomnia, Sedaltine, Sedumax, Slumbrin, Somnosal, Somnotil.

To these may be added ' Relaxa ' and 24 other proprietary preparations, containing these drugs or their derivatives, which are listed by Marler (1958). Prosser Thomas (1958) has pointed out that some drugs not primarily intended as sedatives also contain carbromal—e.g., ' Fydalex ', ' Hyperysin ', ' Menopax ' tablets, ' Menovo ', and ' Viredrin '. In our series, adalin (300 mg. carbromal per tablet) and persomnia (195 mg. carbromal and 65 mg. bromvaletone per tablet) were taken.

Hydrolysis of carbromal and bromvaletone gives urea and the corresponding brom-fatty acid—i.e., diethylbromacetic acid or dimethylbrompropionic acid. The manner of degradation of the brom-fatty acids, with the release of inorganic bromide, has not been established to our knowledge. According to Stöhr (1951), in animal experiments most of the ingested carbromal is excreted in three forms—i.e., inorganic bromide, brom-fatty acid, and an ether-soluble substance containing bromine—and very little is excreted unchanged via the kidneys.

On considering whether the toxic action of carbromal and bromvaletone is different from that of inorganic bromide, as suggested by Sattler (1923), it is difficult to distinguish between their effects on the nervous system and the classical picture of bromism. But two points of difference may be mentioned.

Firstly, carbromal and bromvaletone appear to be toxic to the retina, especially the central area, whereas (according to Stöhr 1951) these changes have not been seen in epileptics who have been treated with very much more inorganic bromide. Secondly, the purpuric skin reaction produced by carbromal in susceptible subjects (Kruizinga 1950, Borrie 1955) is unlike the acneiform eruption of bromism. Herzberg (1927), however, reported a pustular eruption (" bromdermatitis ") in a patient with bromvaletone intoxication. There were no skin reactions in our cases.

Another point of practical interest is the effect of combining carbromal with other hypnotics.

Lovelace and Roith (1955) found that methylpentynol and carbromal did not potentiate each other; on the other hand Chen and Portman (1952) found that pentobarbitone and carbromal were synergistic in their anticonvulsive effects in rats. Moreover, the effects of carbromal are likely to persist longer than those of other hypnotics because of the slow rate of excretion of the inorganic bromide. In two of our cases self-medication was combined with sedative treatment by a physician.

Carbromal and bromvaletone preparations are widely advertised as " safe " hypnotics, but this claim is questionable. The sale of carbromal without prescription has been condemned by Magnussen (1947), and since 1947 has been forbidden in Denmark (*Ugeskrift for Læger* 1947). With others (Barker 1958, Young 1958, Seager and Foster 1958, *Pharmaceutical Journal* 1958a and b) we think the same step should now be taken in Great Britain. It is to be expected that some will disagree with this view (Douthwaite 1958a). Nevertheless, we are surprised that responsible medical opinion should discuss carbromal and bromvaletone (*British Medical Journal* 1958, Douthwaite 1958b) without indicating fully their dangers. Magnussen has seen only a few cases of mild poisoning attributable to bromvaletone alone; on the other hand Stern (1919), Jakob (1924), Sattler (1923), and Lindeberg (1930) report cases in which the effects were very similar to those of carbromal. In view of the close relationship of these two drugs it seems logical to prohibit the free sale of bromvaletone along with carbromal.

Summary

Five cases of carbromal intoxication are reported. Each was characterised by a confusional state, and in two there was coma.

The clinical course after withdrawal of the drug is described, and in the first case details of the bromide and halide levels in the blood and urine are given.

The symptoms of carbromal intoxication are compared with those of bromism.

It is suggested that carbromal and bromvaletone should be available only on prescription.

We are grateful to Dr. D. E. Bunbury, Dr. S. W. Hardwick, Dr. W. L. Neustatter, and Dr. E. M. Stack for permission to include reports on their patients; to Dr. W. A. Caldwell, physician-superintendent of West Park Hospital, for access to case papers; to Dr. Anne May and Dr. Karl Strand for translations of Dutch, German, and Danish papers; and Mr. A. Ogden for pharmaceutical information.

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MOBILISING PATIENTS RECEIVING INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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PARALYSED patients with impaired respiratory function who require intermittent positive-pressure respiration (I.P.P.R.) indefinitely are often confined to bed with corresponding limitation in outlook and interest. Mobility is clearly of great importance to lessen this restriction and improve morale. To provide this it is necessary to have a small but reliable respirator independent of a fixed power source, a stable connection to the tracheotomy tube, a portable suction pump, and a mobile chair that will carry the patient and this apparatus. We describe the equipment that we have found convenient for this purpose.

Respiration Pump

The Radcliffe Respiration Pump (Russell and Schuster 1953) has been modified to incorporate inspiratory and expiratory

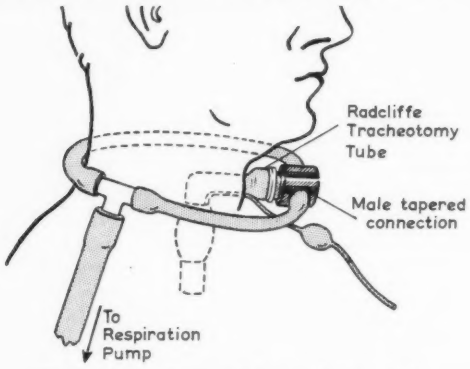

Fig. 1—" Collar " connection to tracheotomy tube.

valves operated by cams, as in the Radcliffe Positive-Negative Pressure Respiration Pump (Russell et al. 1956). This modification eliminates the pressure-operated valve and is more convenient and reliable. The overall dimensions are $16 \times 14 \times 18\frac{1}{2}$ in. ($40 \times 35{\cdot}5 \times 47$ cm.). Power is provided from one of three sources: by 230-volt A.C. motor, 12 volt D.C. motor, or hand operation; and the change from one to another is simple and rapid. Current varies at different parts of the respiratory cycle but does not exceed 3 amperes at 12 volts, and a 12 volt 60-ampere-hour accumulator can be used for 24 hours without recharging. This respiration pump is therefore suitable either in the ward or when the patient is being transported in a wheel chair.

Suction Pump

A foot-operated suction pump is suitable. We have used the Smith-Clarke suction pump; the ' Ambu ' pump may also be satisfactory for this purpose. Sterile catheters are carried in a closed box $19 \times 3\frac{1}{4} \times 3$ in. ($58 \times 8{\cdot}3 \times 7{\cdot}6$ cm.).

Connection to the Tracheotomy Tube

The respiration pump is connected to a Radcliffe tracheotomy tube (Spalding and Smith 1956) by a pipe forming a collar (fig. 1), the male tapered connection being made of plasticised polyvinyl chloride. This provides a comfortable and secure attachment and eliminates drag on the tracheotomy tube.

Mobile Chairs

Two types of chair have been used. In the first a platform of $3 \times 1{\cdot}5$ in. ' Dexion ' has been bolted to the frame of an ' Allwin ' invalid chair, and carries the respiration pump, a 12-volt 60-ampere-hour accumulator, suction pump, and catheter box (fig. 2). The weight is distributed through the

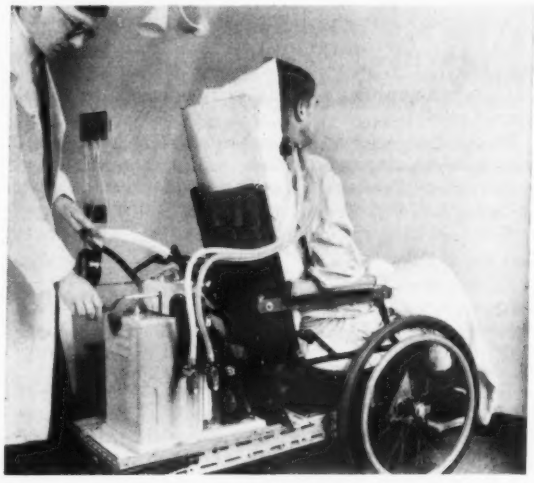

Fig. 2—Respiration pump on a platform attached to a standard type of wheel chair. Hand operation of the respiration pump is shown.

frame and a trailing castor. A humidifier, though not generally required, can be incorporated.

If a severely paralysed patient is to remain in a wheel-chair for a considerable period, the chair must be comfortably upholstered and must give adequate support to his head as well as his trunk. We have found aircraft chairs very suitable for this purpose, and in addition they allow the patient to recline if he is fatigued by sitting vertically. The chair can be mounted on castors or on a lightweight hand-truck, which will also carry the respiration pump and accumulator. In the latter case it may be convenient, especially in large hospitals, to have the truck electrically propelled, and the Geest hand-operated truck model no. 12 TD-$\frac{1}{6}$ H.P. fitted with tractamatic drive makes a suitable mount (fig. 3). If the patient is transferred to a car it may be desirable to use a head-rest attached to the car seat, and these are available from many suppliers of motor-car accessories.

The mobility provided by the means described has had a most beneficial effect on the outlook of patients, enabling them to travel not only about the hospital but also further afield, including visits to private houses.

Summary

Paralysed patients who permanently require artificial respiration can be made mobile.

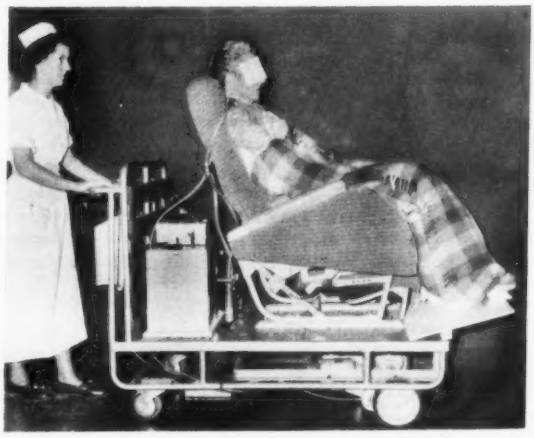

Fig. 3—Aircraft chair, and respiration pump mounted on self-propelled truck.

They require a portable positive-pressure respiration pump, suction pump, firm connection to the tracheotomy tube, and a suitable chair.

Apparatus is described that has proved satisfactory.

The Radcliffe Respiration Pumps are manufactured by Messrs. H. G. East & Co., 37, Oxford Road, Cowley, Oxford; the Smith-Clarke foot-operated suction pump is manufactured by the Cape Engineering Company, Ltd., Warwick. The 'Ambu' pump is distributed by British Oxygen Gases, Ltd., Medical Division, Brentford, Middlesex; the collar was designed and made by Mr. R. H. Salt, of the Nuffield Department of Anæsthetics, Oxford; the aircraft chair was obtained through the Purchasing Controller, B.O.A.C., London Airport; the Geest accumulator-operated truck is manufactured by Geest Industries, Ltd., Spalding, Lincs.

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EXCESSIVE GANGLION BLOCKADE PRECIPITATED BY CHEMOTHERAPY IN PATIENTS WITH CHRONIC PYELONEPHRITIS AND HYPERTENSION TREATED WITH GANGLION-BLOCKING DRUGS

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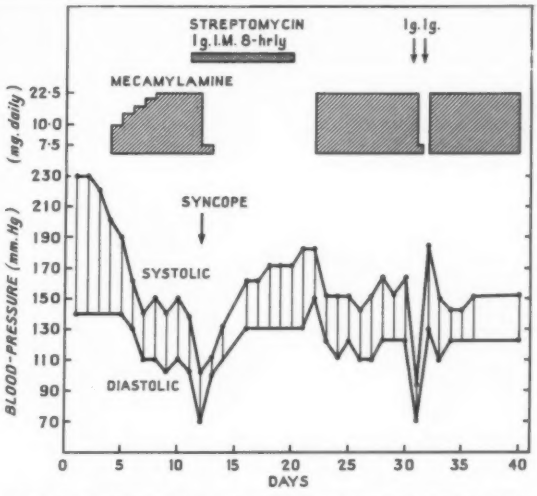
THE hypotension induced by ganglion-blocking drugs may be enhanced in several different circumstances (Smirk 1956). The excretion of mecamylamine is reduced by carbonic anhydrase inhibitors, such as acetazolamide and chlorothiazide (Harrington and Kincaid-Smith 1958). Chlorothiazide is reported to increase the effect of a wide range of hypotensive drugs (Freis and Wilson 1957, Hollander and Wilkins 1957, Tapia et al. 1957).

I show here that the features of excessive ganglion blockade may also occur when an attempt is made to treat chronic pyelonephritis with chemotherapeutic agents in hypertensives who are already taking either pentolinium or mecamylamine.

Cases

The data on four cases of apyrexial, non-obstructive chronic pyelonephritis with severe hypertension are shown in the accompanying table. In case 4 the diagnosis was confirmed post mortem. In the remaining three cases the diagnosis was necessarily largely clinical; but, in the presence of recurrent attacks of loin aching and dysuria, it was thought that little reasonable doubt existed. Pyuria was demonstrated during a symptomless phase at some time during hospital inpatient treatment in all cases.

Each patient was kept in bed and the blood-pressure allowed to settle to a steady level. Pentolinium or mecamylamine was then given orally at 6.30 A.M., 1 P.M., and 6 P.M., and the dose increased to one which would produce an adequate fall in pressure. When, on this dose, the blood-pressure taken three hours later showed little day-to-day variation, chemotherapy was started at 10.30 P.M.



Effect of streptomycin in the presence of mecamylamine on the blood-pressure taken in the standing posture at 9.30 a.m. (case 3).

In all six observations were made—two on each of two patients, and one on each of two patients.

At 9.30 A.M. on the following day, all the patients complained of dry mouth, blurred vision, and malaise; and the blood-pressure, taken in the recumbent posture, was found to be unusually low. To avoid hazard to the patients, they were ordinarily kept flat in bed, thus averting postural hypotension; but the dramatic effect of the standing posture is indicated in the accompanying figure, which shows typical findings. The disturbance lasted approximately twenty-four hours in the absence of further doses of the ganglion-blocking drug, which had to be reintroduced in the original dosage in order to regain control of the blood-pressure even though chemotherapy was continued. Sulphadimidine, streptomycin, tetracycline, and chlortetracycline produced identical effects in the four cases observed. These effects were reproduced, though their duration was briefer, in cases 3 and 4 after ten days and three days respectively, using similar and different combinations of antibiotics and sulphadimidine. In view of the known behaviour of chronic pyelonephritis, this may possibly reflect the inadequacy of the initial chemotherapy or reinfection of the renal parenchyma.

A control group of ten patients with severe hypertension (eight with essential hypertension and two with chronic nephritis) was tested in exactly the same way with a similar combination of drugs; renal function was impaired considerably in six of these cases. In no case was there any subjective disturbance, nor was there any alteration in the blood-pressure readings on the day following the start of chemotherapy.

DATA ON 4 CASES OF CHRONIC PYELONEPHRITIS

Case no.	Age (yr.)	Sex	Retinopathy (Keith-Wagener grade)	Blood-urea (mg./100 ml.)	Max. urine specific gravity*	Catheter spec. urine		
						Pus cells (No./H.P.F.)	Organism	Antibiotic of choice†
1	47	F	2	24	1·020	10–20	*Escherichia coli.*	Sulphadimidine
2	54	M	2	32	1·016	30	*Esch. coli.*	Tetracycline
3	53	F	4	43	1·014	20–30 (gran. casts)	*Staphylococcus aureus*	Streptomycin
4	45	F	4	65	1·008	one mucoid mass	*Streptococcus fæcalis*	Chlortetracycline

*After overnight deprivation of water. †Based on in-vitro sensitivities.

Discussion

In these four patients with hypertension and chronic pyelonephritis the familiar effects of ganglion-blocking drugs appeared to be enhanced by chemotherapy. The absence of enhancement in hypertensive patients who did not have chronic pyelonephritis suggests an intimate association with this process. Further, the brevity of the effect, which was observed only at the start of chemotherapy, suggests that local chemical or physical changes, connected with the initial impact of the chemotherapeutic agent on the inflammatory reaction or its causal organism within the renal parenchyma, may be responsible. Tentatively I suggest that these changes may be found to operate by temporarily reducing the clearance of the ganglion-blocking drug directly or through the release of a vasodepressor substance from the inflammatory reaction of from the organism in the infected kidney.

I have since seen one death, and heard of another, resulting from this phenomenon. Both patients had been living precariously in a state of compensated renal failure and died of uræmia within three weeks of the start of chemotherapy. I suggest that ganglion-blocking drugs and chemotherapy should not be given in combination to hypertensive patients with chronic pyelonephritis.

Summary

The effects of ganglion-blocking drugs may be enhanced briefly by chemotherapy in patients with hypertension and chronic pyelonephritis.

To avoid dangerous hypotension, the chemotherapy of chronic pyelonephritis should not be accompanied by ganglion blockade.

Impaired clearance of the ganglion-blocking drug may prove to be the cause of this phenomenon.

I wish to thank Dr. R. F. Jarrett and Dr. G. R. Fearnley, of the Gloucester Royal Infirmary, on whose patients these observations were made, for their encouragement and helpful criticism. This study was made with the permission and full cooperation of all the patients.

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ORCHITIS ASSOCIATED WITH SPERM-AGGLUTINATING ANTIBODIES

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THE development of heterologous antibodies of high specificity to sperms of man and laboratory animals has long been known (Landsteiner 1899, Metchnikoff 1900). Sperm-agglutinating antibodies have been demonstrated in the sera of a few infertile men (Rümke 1954, Wilson 1954); in some of these patients true autoantibodies were present (Wilson 1954). The injection of guineapigs with homologous or autologous testes or sperms and complete Freund's adjuvants has been shown to produce aspermatogenesis (Freund et al. 1953, 1955). So far there has been no report of sperm-agglutinating antibodies associated with a lesion of the testes in man. It was therefore decided to look for sperm-agglutinins in cases of epididymitis and orchitis, particularly granulomatous orchitis. In this condition there are granulomata involving the seminiferous tubules, and diffuse interstitial inflammation in which plasma-cells are numerous.

Sera from 6 cases of granulomatous orchitis and 8 cases of epididymitis and/or orchitis have been examined. 2 patients were found to have antibodies causing head agglutination of sperms. Both patients have offspring.

Case A (aged 52, group AB Rh+ve) developed a swelling of the right testis early in September, 1958. He complained of a dragging pain in the groin, but the testis was not painful. Orchidectomy was performed in Sept. 30, 1958, and the condition was found histologically to be granulomatous orchitis.

Case B (aged 59, group B Rh+ve) complained of intermittent pain and swelling of his left testis from June to December, 1958. No biopsy was performed, and the diagnosis remains uncertain.

Serological Observations

Slide-agglutination tests were performed by a modification of the technique of Wilson (1954), with twofold serial dilutions of whole serum; with euglobulin, pseudoglobulin, and albumin fractions; and with whole serum after absorption with human group-AB Rh+ve red blood-cells or sperms. The results are summarised in the accompanying table.

TITRE OF SERA AND FRACTIONS

Case	Whole serum	Euglobulin	Pseudoglobulin*	Albumin	Serum absorbed with	
					AB Rh+ve cells	Sperms
A	1/128†	1/64	1/8	—	1/64	1/16
B	1/64	1/32	1/8	—	1/64	1/16

* Traces of γ-globulin were detected on paper electrophoresis.
† Serum obtained 2 months after orchidectomy.

Complement-fixation tests were performed with inactivated whole serum and sperms or seminal plasma. No complement-fixing antibodies were demonstrable.

Precipitin tests using seminal plasma and saline extracts of various organs were negative.

The sera were tested against sperms and sections of normal testis for tissue-localising antibodies by the indirect fluorescent-antibody technique (Weller and Coons 1954), using the patient's serum followed by rabbit anti-human γ-globulin serum labelled with 'Lissamine Rhodamine B200' (Chadwick et al. 1958). No localising antibodies could be demonstrated.

Discussion

These results indicate that the factor in the patient's serum responsible for the agglutination of sperms is concentrated in, if not peculiar to, the γ-globulin fraction and is therefore an antibody. Evidence from other work suggests that such an antibody would react with an autologous as well as with homologous antigen, so that it seems likely that autoantibodies are present in some cases of orchitis. Much further work is obviously necessary to determine the precise nature of the antigen(s) involved and whether the antibodies are pathogenic or merely an epiphenomenon.

This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust. We wish to thank Dr. A. Knudsen, Dr. R. S. Ralph, and Dr. R. M. Ransom for sending serum from cases of granulomatous orchitis.

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THE CHROMOSOMES IN A PATIENT SHOWING BOTH MONGOLISM AND THE KLINEFELTER SYNDROME

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FOR many years the diploid number of chromosomes in normal men and women was believed to be forty-eight. Since the observations of Tjio and Levan (1956) and of Ford and Hamerton (1956), using improved methods, forty-six has been generally accepted as the correct number, twenty-two pairs of autosomes and one sex chromosome pair. The chromosomes of a case of Klinefelter's syndrome, with skin cells exhibiting the Barr chromatin body as in the female, have been studied by Jacobs and Strong (1959) and found to number forty-seven. This was interpreted as the result of the presence of two X chromosomes as well as one Y. The chromosome complement in mongolism was first investigated by Mittwoch (1952) who reported an approximate diploid number of forty-eight chromosomes in spermatocytes. Techniques at that time were not adequate to give exact results. However, Lejeune, Gautier, and Turpin (1959) reported the finding of a small extra chromosome in tissue cultures from the connective tissue of three cases of mongolism, making a total count of forty-seven.

Fig. 1—Mitotic metaphase in a bone-marrow cell.

The patient described here is an imbecile, aged 45, who shows signs typical both of Klinefelter's syndrome and of mongolism. He is fourth in a sibship with three normal sisters. The father was 40 years old and the mother 42 at his birth and they are not consanguineous. The Barr chromatin body is present in cells of the skin and buccal mucosa; leucocytes with drumstick appendages have been identified, as in a normal female. He has small testes, scanty facial, axillary and pubic hair, slight gynæcomastia and feminine distribution of fat. Testicular biopsy revealed advanced atrophy with no spermatogenesis, only ghost tubules and rare interstitial cells. The mongoloid traits are very well marked, including typical palmar patterns, single creases on the minimal digits, fissured tongue, cataract, and slight cyanosis.

Bone-marrow specimens, obtained by sternal puncture, were treated by a modification of the method described by Ford, Jacobs, and Lajtha (1958). Squash preparations were made from the final, Feulgen-stained, cell suspension. These were searched systematically for cells in metaphase of mitosis. More than fifty cells, in which the chromosomes could be counted accurately, were recorded. Each of them contained forty-eight chromosomes. The detailed chromosome morphology was examined carefully in ten cells. Each appeared to contain a normal set of twenty-three pairs, as in a female, with, in addition, a Y chromosome and an extra acrocentric chromosome. There are two very similar pairs of acrocentric chromosomes in the normal complement, one pair probably slightly larger than the other, pairs 22 and 23 of Ford et al. (1958)—alternatively, nos. 21 and 22 of Tjio and Puck (1958). In the present case, these four chromosomes and the additional acrocentric chromosome are almost indistinguishable from one another: it is possible that two are a little longer than the other three. A representative cell is shown in fig. 1. In fig. 2 the chromosomes from this cell are arranged as far as possible in pairs. The five short acrocentric chromosomes are arranged as a pair and a group of three, and the Y chromosome, which, though very similar, is usually distinguishable from them, is shown by itself. Identification of the X chromosome pair is still uncertain: it is believed to be the seventh in order of length and is shown as such in fig. 2.

This appears to be the first time that a human being with two supernumerary chromosomes has been described. He possesses an additional sex chromosome, as found in

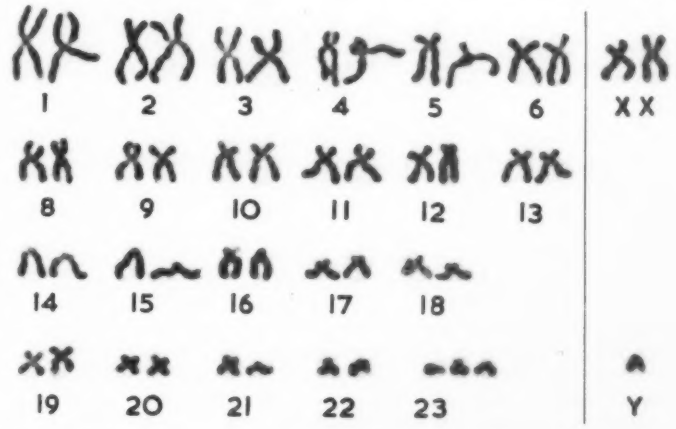

Fig. 2—Chromosomes arranged to size; the X chromosomes are seventh in this order.

Klinefelter's syndrome, and an additional small chromosome which seems likely to be characteristic of mongolism. It is remarkable that the patient's general health should be satisfactory.

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THE SOMATIC CHROMOSOMES IN MONGOLISM

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DURING recent studies of human intersexes it has been found that chromatin-positive cases of Klinefelter's syndrome have a diploid number of 47 and that the additional chromosome is an X chromosome, the chromosome sex in these cases being XXY (Jacobs and Strong 1959, Ford personal communication). These studies were made on marrow cells utilising the technique previously described by Ford, Jacobs, and Lajtha (1958).

Following these studies, and because some cases of Klinefelter's syndrome suffer from mental deficiency (Ferguson-Smith 1958), it was decided to extend such investigations to cases of mongolism. This decision was also conditioned by the reported association between mongolism and leukæmia (Carter 1956, 1958, Krivit and Good 1956, Merrit and Harris 1956, Stewart, Webb, and Hewitt 1958). The presence of an abnormal chromosome number has been reported in one case of acute human leukæmia (Ford, Jacobs, and Lajtha 1958) and further examples of such abnormalities have been found in other cases of acute leukæmia (Jacobs unpublished data, Ford personal communication).

CHROMOSOME COUNTS IN FOUR MONGOLS

Case no.	Chromosome number and number of cells counted					
	44	45	46	47	48	Polyploids
H 114	1	..	2	41	7	3
H 120	..	1	6	26	2	..
H 122	..	1	2	36	1	4
H 125	..	1	1	34	3	3

The somatic chromosomes have been examined in six typical mongols—three males aged 41, 22, and 20 years, and three females aged 20, 20, and 16. Two of the females had congenital heart lesions. The males were chromatin-negative, and the females chromatin-positive, as determined by an examination of blood and buccal smears.

In all six cases the diploid number was found to be 47: detailed counts for four cases are shown in the accompanying table. Deviations from the diploid number are considered to be due to technical errors (Ford, Jacobs, and Lajtha 1958). Lejeune, Gauthier, and Turpin (1959) have also reported the finding of a diploid number of 47 in three male mongol children. It appears, therefore, that the condition of mongolism is associated with the presence of an extra chromosome.

The additional chromosome, as seen in our material and as reported by Lejeune, Gauthier, and Turpin, is an acrocentric chromosome in the smallest size range, where the Y chromosome is also to be found (Ford, Jacobs, and Lajtha 1958, Tjio and Puck 1958). The remaining 46 chromosomes do not appear different from those in the normal diploid set. It is improbable though not impossible that the additional chromosome in mongolism is a Y chromosome. In the case of females, however, this would result in an XXY female, a sex-chromosome constitution known to be associated with chromatin-positive cases of Klinefelter's syndrome. It is known that the risk of giving birth to a mongol is closely related to increasing maternal age (Penrose 1934) and that the mongol child resembles its mother antigenically more closely than its father (Penrose 1957). Both these facts suggest that the primary disorder may lie in oogenesis. If this is so, the extra chromosome is likely to be an autosome. It may well be that mongols are trisomic for one of the smallest acrocentric autosomes. The trisomic condition is recognised as being due to the failure of both members of a pair of homologous chromosomes to segregate during either meiosis to give a haploid set in each gamete, or in mitosis to give rise to two cells of a like chromosome constitution (Swanson 1958). If both chromosomes pass to the same nucleus this may result, in the case of a gamete effecting union with a normal gamete, in an individual with a chromosome number of $2n+1$, the value of n for man being 23. The possibility cannot be entirely excluded at present that the extra chromosome is a supernumerary one. The origin of such chromosomes is unknown: they have been found in a variety of insects and plants, and are said to be of smaller size than other members of the chromosome complement, as well as appearing to be genetically inert (Swanson 1958).

Among the many implications of the reported findings, the association of a predisposition to leukæmia in a group of individuals with an abnormal karyotype is clearly of great interest and potential importance. The significance of this association in relation to possible mechanisms of carcinogenesis—e.g., the two stage mechanism postulated by Armitage and Doll (1957) remains to be elucidated.

We are grateful to Dr. W. M. C. Harrowes for allowing us to study patients under his care, and Dr. N. Maclean for examining the blood and buccal smears. We should also like to thank Miss M. Brunton for technical assistance.

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A SEX-CHROMOSOME ANOMALY IN A CASE OF GONADAL DYSGENESIS (TURNER'S SYNDROME)

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GONADAL dysgenesis (ovarian agenesis, gonadal dysplasia) is a clinical syndrome usually presenting as a failure of secondary sex characteristics at puberty in girls whose gonads are absent or rudimentary. It is often associated with other congenital malformations such as small stature, digital anomalies, and, more rarely, webbed neck, congenital heart-disease, renal anomalies, intellectual subnormality, and other developmental errors. The more extreme expressions are often referred to as Turner's syndrome.

A considerable proportion of patients with gonadal dysgenesis are chromatin-negative (Décourt, Sasso, Chiorboli, and Fernandes 1954, Polani, Hunter, and Lennox 1954, Wilkins, Grumbach, and Van Wyck 1954), although chromatin-negativity (Barr and Bertram 1949) is an invariable feature of normal males. One possible explanation is that gonadal dysgenesis in man is due to castration while an embryo, since the experimental castration of embryonic rabbits results in the production of animals of female phenotype irrespective of the genetic sex-constitution of the embryo (Jost 1947). However, in abnormal individuals chromatin negativity or positivity ("nuclear sexing") may not necessarily indicate true chromosomal sex (*Lancet* 1956, Polani, Lessof, and Bishop 1956). An alternative explanation for the findings in gonadal dysgenesis might be abnormal sex differentiation following anomalous sex determination in the zygote.

Two approaches to the problem of certainly identifying the sex chromosomes present in Turner's syndrome suggested themselves: direct cytological observation, and the study of colour-blindness, which is a sex-linked recessive character and an X-chromosome marker. The results obtained by the second method agreed with the simple interpretation of the "nuclear sexing" results: chromatin-negative patients with gonadal dysgenesis seemed to have only one X chromosome (Polani et al. 1956). The presence or absence of the Y chromosome could not be determined and it was thought likely that the patients had an XY sex-chromosome constitution, although the possibility that they might be XO was also considered. Danon and Sachs (1957) also suggested that some patients with gonadal dysgenesis might have an XO sex-chromosome constitution, but that other patients might be examples of somatic mosaicism in respect of their sex-chromosome constitution. A study of the blood-groups of three patients with gonadal dysgenesis (Platt and Stratton 1956) supplied evidence that these individuals were not haploid—i.e., were not XO merely because all their chromosomes were unpaired.

Technical developments have recently made it possible to obtain accurate information regarding the somatic chromosomes of human patients, either in bone-marrow cells briefly incubated in vitro (Ford, Jacobs, and Lajtha 1958) or in cells from tissue cultures (Tjio and Puck 1958). In consequence the normal number of human chromosomes and their normal morphology are now reasonably well known. The subject of this report is a chromatin-negative case of Turner's syndrome whose bone-marrow cells proved to contain 45 chromosomes only, instead of the normal number of 46, and whose sex-chromosomal constitution is determined to be XO.

Case-report

The patient presented at the age of 14 with a short stature, primary amenorrhœa, and absence of secondary sex characteristics. In addition she was backward at school.

Family history.—Parents healthy. Father 5 ft. 4 in., mother 5 ft. 2 in. A maternal aunt, who died at the age of 21, was dwarfed and had had only two scanty periods; she was known to have pernicious anæmia. Two brothers 6 and 10 years old and one sister aged 9 were all healthy.

Personal history.—Maternal health good during pregnancy, and delivery normal. Birth weight 5 lb. 4 oz. Early development normal.

On examination, height 51 in., lower segment 25 in., arm-span 50 in. Weight 4 st. 13 lb.

There was slight facial asymmetry, low implantation of the ears, and a small chin. There was a high arched palate, a short broad neck without webbing, slight funnel deformity of the chest, cubitus valgus, pes cavus, and digital deformities. Cardiovascular system normal. Blood-pressure 110/70. Normal femoral pulses. There was no evidence of puberty.

Investigations

Examination of skin biopsy and blood smear showed a chromatin-negative pattern.

Follicle-stimulating hormone positive to 32 mouse units 17-ketosteroids 10·8 mg. per day.

Radiographically chest, heart, intravenous pyelography normal. Radiological assessment of bone age corresponded to the chronological age.

No defect in colour-vision (Ishihara) in patient or parents.

The marrow cells, obtained by a routine marrow puncture, were suspended in a mixture of glucose-saline and serum from the patient herself, and were sent to Harwell for cytological processing. After incubation the cells were exposed to colchicine for one hour, then fixed and stained by the Feulgen procedure. Squash preparations were made and the chromosomes were studied in cells arrested in the metaphase of mitosis by the action of the colchicine.

The chromosomes were counted in 102 cells of which 99 cells were found to have 45 chromosomes only. The remaining 3 cells contained fewer than 45 chromosomes and previous experience suggests that the deficiency is likely to be a consequence of damage to the cells during the making of the preparations. 14 cells were selected for detailed study. In every one of them 4 small acrocentric chromosomes were present, as in a normal female: in a normal male there are 5 of these chromosomes, one being the Y chromosome. All the selected cells also contained 15 medium-length metacentric chromosomes, as in a normal male—a normal female having 16 which include the two X chromosomes (Ford et al. 1958). These observations of themselves strongly suggest that the chromosome constitution is XO.

The individual recognition of the X and Y chromosomes may be a matter of some difficulty. However Tjio and Puck (1958) assert that X and Y chromosomes

Fig. 1—Chromosomes (45) of the patient with Turner's syndrome discussed in the text. Colchicine-arrested metaphase in a bone-marrow cell. Feulgen squash preparation (× 2200). The round black body is probably an oil droplet.

can be recognised individually in their preparations made from tissue cultures. We agree that the Y chromosome can be distinguished in favourable cells of normal males, but we have not yet been able to identify the X chromosome (or chromosomes) unequivocally in bone-marrow preparations. Nevertheless in many of the selected cells of the present patient it was possible to make a reasonably satisfactory classification of the chromosomes into 22 pairs and one odd chromosome. A photograph of one of these cells is reproduced in fig. 1. In fig. 2 the chromosomes from the same cell are shown arranged in pairs. Suspicion that the odd chromosome is the X is inevitable, but this chromosome and the two members of pair 6 are very similar in length and arm-ratio and their true relationships remain uncertain. The probability that one of the three is X is strengthened by the good agreement of their proportions with those of undoubted X-chromosomes in X-Y bivalents at metaphase in primary spermatocytes (Ford and Hamerton 1956). Experience of numerical chromosomal abnormalities in animals and plants (Swanson 1957) suggests that it is very improbable that a human individual who has only 45 chromosomes as the result of the loss of a large or medium-sized autosome would be viable, but that an XO zygote might well develop to maturity. We therefore conclude that the sex-chromosome constitution of the patient is XO.

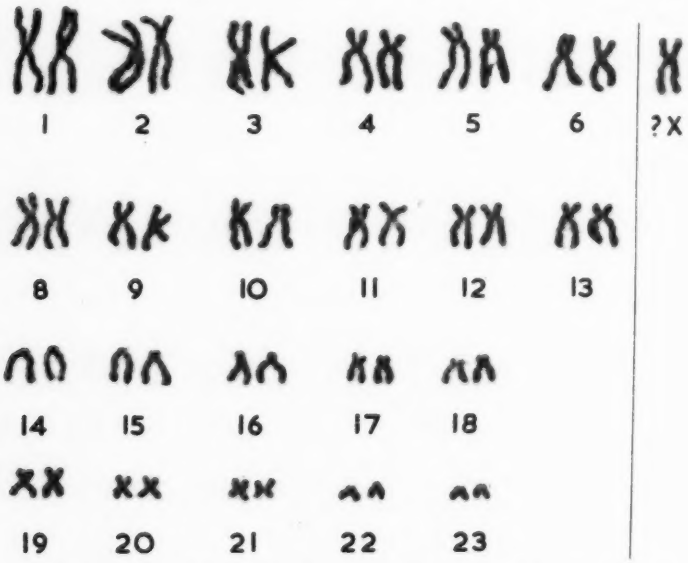

Fig. 2—Chromosomes from the cell shown in fig. 1 arranged in pairs (× 2200).

Discussion

These observations are of interest not only with reference to Turner's syndrome. Here is an individual who is female anatomically and psychologically, whose cells are " male " as judged by nuclear sexing, and whose chromosomes are neither normally male nor normally female. However, as judged by her chromosomes she has no male component, but half a normal female component, and there seems no justification for considering her to be really male in any sense. It must therefore be accepted that chromatin negativity does not necessarily imply maleness and it would probably be best if the phrase " nuclear sexing " were dropped from the vocabulary and the more accurate if less striking terms, chromatin negativity or positivity, were always used instead. The very real clinical reasons for doing this have already been stressed.

An explanation of the origin of the sex chromosome anomaly in gonadal dysgenesis can be sought in the process of non-disjunction, best known as an abnormality of oogenesis in *Drosophila melanogaster* (Morgan, Bridges, and Sturtevant 1925). Non-disjunction of the sex-chromosomes in the female fly implies the migration of two X chromosomes to one pole of the spindle during one of the two meiotic anaphases. Thus the ovum comes to contain either the haploid number of autosomes plus *two* X chromosomes, or only the haploid number of autosomes *without* X chromosomes. Fertilisation of an ovum of the latter type by a Y-bearing sperm results in a non-viable YO zygote; fertilisation by an X-bearing sperm yields an XO zygote which develops into a sterile male. Our findings suggest that in man an XO zygote develops into a sterile " agonadal " individual whose phenotype is female.

Fertilisation of the other type of abnormal ovum (XX) by an X-bearing sperm gives, in drosophila, an XXX zygote with poor viability, but which occasionally survives pupation and then emerges as a fly with accentuated female secondary sexual characteristics, technically called a " super-female "; fertilisation by a Y-bearing sperm yields an XXY zygote which develops into a fertile female. In man the XXX state is as yet unknown, but evidence that the XXY individual appears as a chromatin-positive case of Klinefelter's syndrome has been presented (Ford, Polani, Briggs, and Bishop 1959, Jacobs and Strong 1959.) The evidence in favour of

the occurrence of non-disjunction in man is thereby strengthened.

Non-disjunction has so far been considered as occurring during oogenesis only. Family colour-vision studies in cases of gonadal dysgenesis suggest that it may also occur during spermatogenesis. If an O ovum is fertilised by an X sperm and the resultant individual has a major red-green colour-vision defect, the father should also show the colour-vision defect. But in four families where patients with gonadal dysgenesis (chromatin-negative) have a major red-green colour-vision defect this was not the case (Lenz 1957, Stewart 1958 personal communication; and two of our families, see Bishop et al. 1959). It would appear that in these patients the X-chromosome with the anomalous colour-vision gene was not of paternal origin but was derived from a heterozygous (carrier) mother. These patients have not been examined cytologically, but, if they are XO, it will follow that they developed from zygotes arising from the fertilisation of normal X-bearing ova by sperm carrying neither X nor Y. Such sperm would arise as a result of non-disjunction during spermatogenesis. Evidence that this is by no means unlikely is provided by the observation that X and Y chromosomes are sometimes unpaired at metaphase in first spermatocytes (Ford and Hamerton 1956). Both chromosomes would then be expected to migrate to the same pole in approximately 50% of the ensuing anaphases.

In conclusion it should be emphasised that the XO patient should not be referred to as an instance of "sex-reversal", as a "chromosomal male", or as a "genetic male": she is a female, with an abnormal genotype.

We wish to thank Dr. P. M. F. Bishop for permission to study a patient under his care. We acknowledge the skilful technical assistance of Mr. G. D. Breckon, Miss P. A. Moore, and Miss S. R. Wakefield.

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New Inventions

A PERISCOPIC VIEWER

DURING the study of a postmortem series of bladders, an instrument was constructed to allow the bladder outlet to be seen and photographed from above under measured internal pressures of water.

I thought that, in a modified form (fig. 1), this instrument might be of help to control the degree of tightening during certain retropubic operations on the bladder neck in cases of enuresis and incontinence of urine. The modification has now been completed and used in several anæsthetised patients. It takes the form of a simple periscope of metal tubing with a glass window at each end. Each limb of the periscope is about 2 in. long and of $1^1/_4$ in. diameter. The fundus of the bladder is opened and sutured round a grooved flange in the instrument to make a watertight joint. The periscope mirror reflects the image of the bladder-base region vertically. Illumination is by a small electric bulb (fig. 2).

Fig. 1—The periscope.

Two tubes are led into the bladder through the instrument. One is used for filling the bladder and the other for manometry. The wires for the electric bulb are contained in a tube with plug-in electrodes as in a standard cystoscope of modern type.

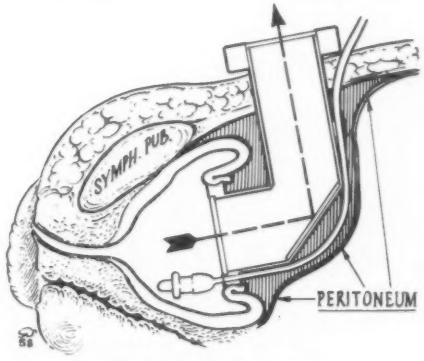

Fig. 2—The periscope in situ.

With this instrument a view of the bladder outlet can be obtained, and cinephotography of the bladder neck under measured internal pressures is possible. It can be left in situ, in an attempt to show the correct degree of tightening, while the operation is in progress. If it gets in the way it can easily be removed and reinserted later if necessary. A tied-in cystoscope is not nearly so easy to use, and photography is impossible except with expensive and specialised instruments. With this viewer one can see a wide area of the bladder-neck region as the operation proceeds. The electric bulb can be grossly overloaded for a short time for photography.

It must be emphasised that both the viewer and some of the operations for which it has been designed are still in the experimental stage.

Because of the view obtained, often well down the urethra, it has been modified to contain a movable diathermy electrode for use at the bladder neck and in the posterior urethra.

I am indebted to Mr. George Smyth, the artist at the Royal Victoria Hospital, Belfast, for the diagram.

The instrument was made for me by the Genito-Urinary Manufacturing Company.

S. A. VINCENT F.R.C.S.

Belfast City Hospital

Reviews of Books

Thirst

Physiology of the Urge to Drink and Problems of Water Lack. A. V. WOLF, PH.D., chief of the renal section, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D.C. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958. Pp. 536. 95*s*.

THIRST is one of the most important physiological responses, and abnormal thirst is a common symptom in disease; but textbooks and monographs until recently gave little help to the physiologist or the clinician seeking knowledge about thirst. This book makes up for past deficiencies. Dr. Wolf, who has made fundamental contributions to the study of thirst, has reviewed practically all that has been written on it and has also provided many lengthy extracts from original texts. The book is thus both an encyclopædia and an anthology of thirst.

The author's style does not make for easy reading, and the profusion of his sources sometimes makes it hard to judge between conflicting theories. These criticisms, however, detract little from the value of the book as a work of reference, not only on the problems of thirst and the need for water but also on such questions as the regulation of the volume of the body fluids or the survival of castaways. Anyone who looks through the table of contents is certain to find something to interest him—by satisfying his curiosity, for example, about ethyl alcohol as a " dipsogen " or about water deprivation in the desert or at sea.

The Rorschach and the Epileptic Personality

J. DELAY, P. PICHOT, T. LEMPERIÈRE, J. PERSE. Translated by RITA and ARTHUR BENTON. New York: Logos Press. 1958. Pp. 265. $6.

THE original work in this book will be comprehensible only to those psychologists who themselves use the technical terms of Rorschach analysis; and the theories it contains will be appreciated only by those who have experience of personality disorders in epileptics. Although the subject is relatively small the literature is copious. The authors do good service in summarising the 77 major papers on this subject. These summaries and the list of references will be useful to PH.D. students working on it.

Since the time of Aretæus the existence of a personality disorder peculiar to epilepsy has been asserted by some and denied by others, and this book could not be expected to solve the problem. The whole concept of epilepsy as a unitary disease (or as two diseases, the symptomatic and the idiopathic) is now dissolving. When fresh crystallisation takes place, it seems likely that many distinct epileptic syndromes will be recognised. Even then we cannot hope to deduce the personalities of our patients merely from their neurological diagnoses.

Showing inkblots to epileptic men and women sometimes reveals an aspect of psychopathology. But a laboratory test of personality is an attempt to stick a pin through that butterfly, Psyche, when she is fluttering in the net: even if the attempt succeeds it leads only to a glass case on the museum shelf. Psyche, metamorphosed, continues her flight, amazing and delighting those who care for her.

Doctor in the Asian Beyond

THOMAS A. DOOLEY. London: Gollancz. 1959. Pp. 224. 16*s*.

IN 1955 the author, then in his late twenties, was serving with the American Navy in North Vietnam and caring for refugees. On his return home he determined to set out on a mission of mercy to a remote and primitive region of Asia. Sustained by a deep religious conviction he chose the kingdom of Laos, once part of French Indochina, and this lively book tells something of his remarkable work and adventures. In some villages there was cholera, in others dysentery, everywhere scabies, ringworm, beriberi, the alternating fevers of malaria, intestinal worms, and yaws—and always the threat of wild beasts. Tact was called for as well as medical and surgical skill. The witch-doctors put a " hex " on the hospital:

" No one, no matter how desperately ill, would come near our hospital for help. These witch-doctors were all respected village elders. But our two most formidable adversaries were Old Joe and a crone we called Maggie. So we decided to adopt an old American stratagem—if you can't lick 'em, join 'em. Instead of antagonising the witch-doctors (and this may raise the hackles of the American Medical Association) we began to treat them as colleagues in the healing arts who practised a somewhat different discipline of medicine with which we disagreed and yet respected."

Their success was complete.

" From that time on Old Joe rarely missed a sick-call. We would administer a shot of penicillin. Joe would invoke the proper spirits. We would splint a fracture, then permit Old Joe to tie the indispensable red, white and black strings around the splints. If we were paid two coconuts for fee, Old Joe received one."

Dr. Dooley's aim throughout was to teach the local people to run their own medical services.

Bacterial and Mycotic Infections in Man (3rd ed. London: Pitman Medical Publishing Co. 1959. Pp. 820. 63*s*.).—This is the third edition of the standard textbook edited by Dr. René Dubos to be published within ten years, and that in itself is a worthy testimonial to its distinguished editor and to the National Foundation for Infantile Paralysis whose subsidy ensures a very reasonable price. The new edition contains more than its predecessors, but its size and weight are about the same, owing to closer printing and the loss of a few references. The plan of the book is almost unchanged, but about half the articles have been put into fresh hands and all have been brought up to date. It would be ungenerous to grumble at these changes, but it is sad to lose Francis's article on Parasitism and Disease. Gertrude Kalz no longer shares the chapter on Applied Medical Bacteriology with E. G. D. Murray, but it remains one of the most original and refreshing. This is probably the best students' textbook of bacteriology on the classical model. In plan it does not differ essentially from Muir and Ritchie (2nd edition, 1899) or Macé's *Traité pratique de bactériologie* (1904). Topley and Wilson had no great interest in systematics, but they arranged their contents with some regard to the accepted Linnæan classification: the authors in " Dubos " skip from streptococci to mycobacteria to staphylococci without obvious design except to put the longest chapters first. The classical textbook certainly helps the student to pass his examinations, but too much attention to the parasites is liable to mask the vital truth that for doctors bacteriology is only a special instance in general pathology.

Biochemistry in Relation to Medicine (3rd ed. London: Longmans, Green. 1959. Pp. 628. 50*s*.).—The new edition of the now well-known book by Dr. C. W. Carter, Dr. R. V. Coxon, and Prof. R. H. S. Thompson has been given fresh life and a wider appeal by the inclusion of two more authors and the omission of most of the practical exercises, which, it was felt, were a little parochial. New chapters on the digestive secretions, intestinal absorption, endocrines, electrolytes, and renal function are welcome, and most of the book has been carefully scrutinised or rewritten. Many new references to original papers have necessarily been added, but the authors have wisely continued to keep these within reasonable bounds. A bit of revision here and there might have improved some of the older chapters, but this edition is a creditable piece of work, which should remain for some time as the useful approach to fundamental medicine it was originally designed to be.

Poisoning by Drugs and Chemicals (London: Alchemist Publications. 1958. Pp. 209. 25*s*.).—The industrial medical officer will find this alphabetical guide to modern poisons, by Mr. Peter Cooper, F.P.S., worth a place in his surgery, and the general practitioner or house-officer who feels the need for an up-to-date detailed guide to poisoning by drugs and chemicals (whether therapeutic, industrial, cosmetic, household, or botanical) will also find here what he requires—though for the most part he may continue to rely on the notes in the *National Formulary*.

Textbook of Physiology and Biochemistry.—In our review (March 14) of this book published by E. & S. Livingstone we gave the price as 65*s*.: it is in fact 63*s*.

THE LANCET

LONDON 4 APRIL 1959

The Chromosomes of Man

THREE related papers which we publish this week are some of the first fruits of a technical advance which may revolutionise human genetics. The science of genetics involves three separate things; and so far, in man, only the first of them has been fruitful—namely, the observation and statistical analysis of inheritance. The second, the cytological study of gene-carrying structures (chiefly chromosomes) in dividing cells, has been carried out mainly in the species in which it was technically easiest, and very little has been achieved in man, or indeed (relatively speaking) in mammals generally. Hence the third and crowning element of genetics, the correlation of inheritance with cytology—that extraordinary process by which we can deduce in drosophila not only the chromosome but the exact spot in the chromosome where each gene lies—has no counterpart in man. Most of what we glibly assume about the physical basis of human inheritance is derived by analogy from the study of very different species. With the exception of the sex chromosomes (whose action we are far from understanding completely) we cannot confidently point to a single fixed point on the chromosome map of man.

The difficulties have been purely technical. The chromosomes of man, as of other mammals, are very hard to study. Meiosis has long seemed the right road; but this, besides being in practice possible only in males and requiring a testicular biopsy, has proved as delusory so far as the north ridge of Everest. The Western Cwm has been provided by the study of mitosis in tissue cultures. Though much valuable work was done soon after the war by HSU,[1] a whole series of cumulative improvements were necessary before significant results began to appear [2 3]: improvements in the Feulgen stain, the delightfully simple " squash " technique of making preparations, the use of the hypotonic saline or citrate to expand the cell and separate the chromosomes, and the use of colchicine were all essential, and all needed critical handling. The effect of colchicine on mitoses is not only the familiar one of halting them half-completed, so that more become available for inspection: its inhibition of spindle formation is far more important, because it prevents the crowding of chromosomes on the spindle, which is the bane of all mammalian chromosome-counts. Colchicine chromosomes, properly treated, are curious objects. Each of them consists of a pair of chromatids, held together only by the centromere. The limbs bend away from the point of attachment; so if the centromere is near the middle (metacentric) the whole structure is X-shaped, and if the centromere is near the end (acrocentric) it is V-shaped. In studying the photographs reproduced on pp. 709 and 712, it is important for the uninitiated to remember that each X-shaped object is a single partly split chromosome, not a chromosome pair: the other member of the pair may lie anywhere within the group. In matching chromosomes, their size and the position of the centromere are the principal points of distinction, and it can readily be seen that differences among them are very considerable. Some five individual pairs can be identified with certainty, a few others less certainly: eight pairs in the middle range of size, all with metacentric centromeres, are unfortunately very hard to tell apart, and they include the X chromosomes.[4]

The first triumph of the new methods was the now familiar demonstration [5 6] that man has 46 chromosomes —not, as had been believed for over thirty years, 48. The second, now in progress, has been the demonstration of clinically significant deviations from that number. This has been greatly facilitated by a further technical advance, the use of very short-term cultures of sternal marrow,[4] with great saving of time and expense and complete elimination of the chromosomal anomalies which are to be expected in tissue cultures maintained for any length of time. The results reported this week were all obtained by this method, worked out by Dr. C. E. FORD and his collaborators at Harwell, and still (so far as we know) used in only two or three laboratories, all in this country.

It had always seemed probable that the anomalies of sexual differentiation uncovered in the past few years by the method of nuclear sexing would prove to reflect some chromosomal aberration, and it is thus not surprising that two of the three conditions in which positive findings have come to light lie in this field. Cases of chromatin-positive Klinefelter's syndrome have very recently been reported elsewhere,[7 8] by the groups contributing to our present issue, to have 47 chromosomes as the characteristic number. One of the papers we publish describes the finding of 45 chromosomes in a case of chromatin-negative Turner's syndrome. Additional cases of both conditions have been seen by both the London-Harwell and the Edinburgh groups, some of them having been reported to the Genetical Society and the Medical Research Society, and it can be taken that these numbers are present in all cases of the two diseases. It appears that in each case it is the sex chromosomes which are at fault, Klinefelter's cases being XXY, and Turner's XO. One cannot be certain of this, for the fault *might* lie in one of the two pairs of autosomes that resemble the Y chromosome, or in one of the seven pairs that resemble the X. But in fact these resemblances are not so exact as caution paints them: in ideal circumstances the Y chromosome can be recognised with near certainty, and the X at least narrowed down to two or three pairs at most. Moreover, it would be straining

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2. Ford, C. E. *in* Symposium on Nuclear Sex, London, p. 13, 1957.
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fortuity rather far for the anomalies to have occurred in both diseases in the appropriate chromosome groups. Several conclusions of great interest follow at once from these findings. Those who have maintained that the sex chromatin represents the XX chromosome pair, but gives no other indication of the state of the nucleus, have been fully justified. The warning we once gave [9] against the indiscriminate use of the term " sex reversal " has been vindicated in a way we never expected; for one cannot regard as sex reversal a case in which the original sex is indeterminate.[10] (Indeed, the necessity for a reform of nomenclature in this field is more than ever apparent.)

Is an XXY a female with an extra Y, or a male with an extra X: is an XO a male with lost Y, or a female with lost X? There may well be answers to these questions (sex ratios of sibships might provide it); but until they are settled we cannot continue in our old assumptions. Perhaps most important of all, however, is the clear evidence that Y is after all no mere useless vestige. If it were, XXY would be a normal female (as it is in drosophila) and XO a normal male. It seems now impossible to avoid the view that it must carry some active masculinising genes. On top of this comes the suggestion [8] that one of the cases of Klinefelter's syndrome investigated is a mosaic, with an admixture of cells with normal 46 chromosome complement and of the commoner 47's. (The second of the Edinburgh mongols, in the paper on p. 710, gives a rather similar count: could it conceivably be a mosaic also?) One of the more exciting possibilities presented by this apparent mosaic is the suggestion that the XX clone represents a viable mutation *back to normal*.

To most people the findings in mongolism, presented in two of our papers today, will seem more surprising than the two aspects already mentioned. Yet we believe that Professor PENROSE had considered the possibility of a chromosome anomaly in this disease twenty years ago. Miss JACOB and the Edinburgh group were led to the same idea by consideration of the incidence of leukæmia in mongolism, and of mental defect in Klinefelter's syndrome. And in fact it cannot be so surprising, for yet a third French group have, for reasons so far unspecified, also thought it worth investigating mongolism, and, using the more laborious tissue-culture technique, were very recently first in the field, reporting the same finding in 3 cases.[11] All cases so far investigated have had 47 chromosomes, the extra chromosome belonging to one of the two small autosome pairs that closely resemble the Y. (It is fairly certain that this extra chromosome is the result of tripling of one of the normal pairs, and not, as LEJEUNE et al. call it, a supernumerary in the true sense of something quite extraneous to the normal complement.) What is certain is that it is not an extra Y, which on purely morphological grounds at least it might almost have been; for Professor PENROSE has provided a case for the first of our papers which, with a patness fantastic at this early stage of the investigation, presents simultaneously the lesions of Klinefelter's syndrome and mongolism, and has both extra small chromosomes, 48 in all.

In this new field of investigation one of the least necessary questions to ask is What next? Positive results have been found in a surprisingly large proportion of the conditions looked into so far: it is unbelievable that there are not many more to be found. It is not entirely accidental that both the Harwell and Edinburgh laboratories are at least nominally concerned primarily with irradiation effects, and leukæmia and some other generalised neoplastic or preneoplastic conditions are an obvious field. But all the intersexes, all forms of mental defect, most hereditary and congenital disorders—these and many other things may be associated with chromosome defects. The cream will be skimmed by those who can best guess which conditions are in fact so associated. But there is an enormous territory awaiting exploitation, with nothing less than the first real explorations of the human chromosome map as the prize if this early promise is even half fulfilled.

9. *Lancet*, 1958, i, 89.
10. See Polani, P. E. *ibid.* March 21, 1959, p. 629.
11. Lejeune, J., Gauthier, M., Turpin, R. *C.R. Acad. Sci., Paris*, 1959, **248**, 602.

New Light on the Lymphatic System

THERE could be no more fitting subject for a Hunterian lecture than the lymphatic vessels,[1] which attracted the interest of both JOHN and WILLIAM HUNTER [2]. In 1784 WILLIAM HUNTER (whose anatomical collection includes beautiful specimens of mercury-injected lymphatics) accurately summarised their function:

" The lymphatics ", he stated, " are the absorbing vessels all over the body. This system only, does absorb and not the veins. It serves to take up and convey whatever is to make or to be mixed with the blood, from the skin, from the intestinal canal, and from the internal cavities or surfaces whatever."

Today it is known that the lymphatics share with the capillaries the regulation of tissue-fluid and are in particular responsible for the absorption from the tissue spaces of particles of high molecular weight—20,000 or over, which includes the extravascular protein. This particulate absorption is the basis of the intravital staining of lymphatic vessels. The anatomist has always been intrigued by the lymphatics, which elude his normal techniques of investigation, and each generation since Renaissance days has devised some new way of displaying them.

In his lecture [1] TURNER-WARWICK gave an up-to-date account of the various techniques for studying the structure and function of lymphatic vessels, whereby we have obtained knowledge of drainage areas which is important in connection with malignant disease, the reaction of lymphatics in inflammation and the different forms of œdema, how they are regenerated in the healing process, and their part in tissue antigen/antibody reactions.

According to TURNER-WARWICK, the ideal substance for intravital demonstration of lymphatics in a specimen would be non-toxic, diffusible, and colourless and of relatively high molecular weight, and once

1. Turner-Warwick, R. T. *Ann. R. Coll. Surg. Engl.* 1957, **24**, 101.
2. Hunter, W. Two introductory lectures to his last course of anatomical lectures at Windmill Street, 1784. J. Johnson, London; p. 58.

in the lymphatics would remain there during the fixation and clearing of the specimen when it would be possible to precipitate it into a particulate colour. He has obtained useful results with iron compounds, such as iron dextran (' Imferon ') and iron saccharate, and subsequent fixation of the specimen with a fluid containing potassium ferrocyanide. The illustrations of lymphatic vessels in most anatomical textbooks are based on the diagrams of JAMIESON and DOBSON,[3] who injected Gerota's mass (containing prussian-blue) into human fœtuses where the lymphatics were dilated following postmortem changes. MCMASTER and HUDACK [4] devised an elegant technique for displaying the lymphatics in the ear of a mouse by injecting different dyes with a special micropipette. From examination of the transilluminated ear in the living animal they reported that the permeability of lymphatic capillaries from within out was similar to that of blood capillaries. By the same injection techniques MCMASTER [5 6] showed the effect of posture and various forms of obstruction to the lymph-flow in a normal human limb, and in patients with cardiac and nephritic œdema, and he also described the repair of lymphatic vessels after making incisions in the skin of the mouse's ear. PULLINGER and FLOREY [7] injected the lymphatics of the mouse's ear with carbon in fine suspension (hydrokollag), and, examining sections after swelling of the tissue had been induced, showed that the lymphatics were attached to adjacent tissue by many fibres which caused dilatation of the lymphatic vessels with any increase in tissue-fluid—for instance, in inflammation. A similar injection technique was used by MILES and MILES [8] in their study of the effect of experimentally produced infections on the lymphatics in the ear of guineapigs and mice. They concluded, unlike MENKIN,[9] that there was no evidence of lymphatic blockade as a mechanism of defence against the spread of infection.

The anatomical distribution of the lymphatic vessels indicates the direction of spread of malignant disease, and TURNER-WARWICK describes a technique of intravital staining by an intramammary injection of 1 ml. of 3% solution of patent-blue or Evans-blue which shows up the lymphatics at the operation site in mastectomy. Such a display of the potential spread of metastases certainly encourages the surgeon to make a clean sweep of all obvious lymphatic vessels and nodes. After a lymphatic vessel has been made visible by injection of a dye into the tissues, diodone injected into the visible lymphatic vessel will provide the contrast for lymphangiography; and radiographs will then show, for example, the tortuosity of lymphatic vessels in elephantiasis.[10]

Work by ALLEN [11] on the penetrability of lymphatics —particularly those of the diaphragm—has reawakened interest in the question of the way in which large particles (in this case paraffin asphalt spheres up to 22·5 μ in diameter) get into lymphatic vessels. Such particles have to penetrate a triple-layer membrane of peritoneal mesothelium, fenestrated basement membrane, and lymphatic endothelium. ALLEN suggests that, as the membranes are stretched with movements of the diaphragm, openings appear between the cells, but continuity is restored when the tension on the lymphatic wall is released as the diaphragm contracts. Though there are objections to this concept of an elastic sieve mechanism, there is no alternative satisfactory explanation. The existence of ultramicroscopic pores 35–40Å in diameter confined to the intercellular cement regions could, PAPPENHEIMER [12] believes, account for the permeability of lymphatic vessels to particles of molecular dimensions. There are, however, other methods of transport through lipid membranes. Already electron microscopy has revealed discontinuities in the endothelium of the kidney glomeruli, and ring-like pores 800Å in diameter are found in some nuclear membranes; and by electron-microscopic examination it should be possible to detect any structural differences between the endothelium of blood and lymphatic capillaries.

Two of our new biological tools have been applied to the study of lymphatics—the radioactive tracers and fluorescein. TURNER-WARWICK describes a method of checking regional lymph drainage by the use of radioactive colloidal gold (^{198}Au), about 10% of which is taken up by the lymphatic system from the tissues. Scintillation counters can thereafter register concentration of the isotope in the regional lymph-nodes, or, more satisfactorily, autoradiography of thin dissected specimens picks out the active regional node. In a study of the lymphatic repair of grafted skin SCOTHORNE [13] used iodinated (^{131}I) human serum-albumin; the presence of the isotope in a regional lymph-node, demonstrated by the scintillation counter, indicated the restoration of lymphatic circulation. EGDAHL and VARGO [14] studied time taken for repair of lymphatic circulation in grafts by injecting fluorescein intradermally and testing the intradermal weals thus formed at intervals with ultraviolet light. With a healthy lymphatic circulation the weals disappear in three to eight hours, leaving only a pinpoint of fluorescein along the needle tract. Fluorescein disappears completely from a primary homograft in five days—that is, about the same time as from normal skin. At ten days, however, a primary homograft will retain intradermal fluorescein for up to forty-eight or more hours, indicating the breakdown in lymphatic circulation preceding the inevitable destruction of the homograft.

These are but a few examples of the kind of biological and pathological information obtainable by intravital staining and other methods of showing lymphatic vessels. Today, when " fluid balance " concerns so many, the lymphatic vessels have become something more than a challenge to anatomists.

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Triamcinolone

POWERFUL modern drugs are mixed blessings, as is clear from experience with the steroids. While in many diseases the administration of steroids is undoubtedly life-saving, in others their exhibition and dosage tax the physician's skill to the full. As with most new drugs, the toxic effects of the steroids have been defined only after their therapeutic action was recognised. After nearly two years' clinical experience with triamcinolone (9-α-fluoro-16-hydroxy-prednisolone) it should be possible to assess its value.

FREYBERG et al.[1] reported 89 cases of rheumatoid arthritis treated with triamcinolone, noting that activity of the disease was usually suppressed by maintenance doses of 10 mg. daily. Peptic ulceration and osteoporosis seemed less common than with prednisolone. On the other hand, DUDLEY HART et al.[2] found that there was little to choose in the incidence of troublesome side-effects. It is nevertheless useful to have this further steroid for patients with rheumatoid arthritis, particularly as it causes less œdema and salt retention than its forerunners.[1 3] Thus triamcinolone is particularly valuable in cases with cardiac disease or in patients œdematous as a result of administration of other steroids.

Many dermatologists have found that triamcinolone is the most useful of the steroids in the treatment of various skin diseases. REIN et al.[4] concluded that it was superior to prednisolone in atopic dermatitis, dermatitis herpetiformis, and exfoliative dermatitis; but their series was small, and the period of observation ranged up to only fourteen weeks. Similar results were obtained by KALZ,[5] who found that the beneficial effect could be maintained by long-term administration. In 60 patients with psoriasis, triamcinolone generally gave a remission in a dose ratio of 4 mg. to 10 mg. of prednisolone.[6]

The first clinical trials of triamcinolone referred briefly to side-effects not previously noted with steroids—postprandial flushing, headache, weight loss, and muscle weakness. Of FREYBERG's 89 patients 11 complained of muscular fatigue. On an earlier page of this issue Dr. R. S. WILLIAMS describes 3 cases of triamcinolone myopathy in which electromyography yielded evidence of a severe muscle-fibre lesion; the myopathy seemed to be similar to that induced in animals by massive doses of cortisone. In these 3 patients the dosage of triamcinolone was higher than that usually employed; and a similar serious myopathy has yet to be reported in a patient given less than 12 mg. daily, which many regard as the maximum " safe " dose. It is encouraging that in 2 of the 3 patients the myopathy improved when triamcinolone was replaced by prednisolone; in the 3rd assessment of change in the myopathy was difficult because the patient's condition was progressively deteriorating. Triamcinolone myopathy of this extent must be rare, but it should be considered in any patient receiving the drug who complains of muscle weakness and in whom the serum sodium and potassium levels are normal (although a normal serum-potassium may occasionally mislead by failing to reflect electrolytic changes in the cell); an early change to another steroid might prevent serious weakness.

In conjunction with WILLIAMS' report, the paper by Dr. MACLEAN and Mr. SCHURR (which also appears in this issue) is of special interest. They describe a patient in whom muscular paralysis developed during treatment with fludrocortisone, which, like triamcinolone, contains a fluorine atom in the 9-α position. The condition of this patient, who had been taking 0·5 mg. of fludrocortisone daily for over a year, improved dramatically within three days after this drug was replaced by cortisone.

Of the other side-effects of triamcinolone, one of the most serious is loss of body-weight. ROBINSON and ROBINSON [7] report that of 14 patients with rheumatoid arthritis who received this drug, 10 lost weight, the average loss being 8–9 lb. None of these patients had obvious retention of water due to previous administration of other steroids; but at least some of the weight loss may have been due to diuresis, particularly as the loss was greatest in the first week of triamcinolone treatment.

Clinical experience suggests that this drug has a valuable place among the steroids, particularly in dermatology; some clinicians regard it as the first choice in the steroid therapy of psoriatic arthropathy. Fortunately the side-effects peculiar to triamcinolone seem to be rapidly reversible; and in the long run they will probably cause less anxiety than that bugbear of all steroid therapy—the development of peptic ulceration.

1. Freyberg, R. H., Bernsten, C. A., Hillman, L. International Congress on Rheumatic Diseases; Toronto, June 25, 1957.
2. Hart, F. D., Golding, J. R., Burley, D. *Lancet*, 1958, ii, 495.
3. Hartung, E. F. *J. Amer. med. Ass.* 1958, **167**, 973.
4. Rein, C. R., Fleischmajer, R., Rosenthal, A. L. *ibid.* 1957, **165**, 1821.
5. Kalz, F. *Canad. med. Ass. J.* 1958, **79**, 400.
6. Shelley, W. B., Harun, J. S., Pillsbury, D. M. *J. Amer. med. Ass.* 1958, **167**, 959.

Annotations

LONG-TERM ANTICOAGULANTS AFTER CARDIAC INFARCTION

JUST over twelve months ago we reviewed progress in assessing the value of long-term anticoagulant treatment for the aftercare of patients who had had cardiac infarction due to ischæmic heart-disease.[8] The evidence from several quarters showed that this treatment was likely to reduce the risk of further infarction and thromboembolic complication and so reduce the overall mortality. We concluded that the time had come when serious consideration might be given to making arrangements for giving this form of treatment to all patients who survived the initial attack of cardiac infarction; and we pointed out that its control would entail provision of facilities that hardly existed anywhere on the scale likely to be needed.

These views are now strongly reinforced by the report to the Medical Research Council of the working party on anticoagulant therapy in coronary thrombosis, published last week in the *British Medical Journal*.[9] This working party, with Sir George Pickering as chairman,

7. Robinson, C. E., Robinson, H. S. *Canad. med. Ass. J.* 1959, **80**, 245.
8. *Lancet*, 1958 i, 417.
9. *Brit. med. J.* March 28, 1959, p. 803.

has dealt specifically with the assessment of long-term anticoagulant therapy after cardiac infarction. The criteria for inclusion in the trial were strict: the patients were aged 40–69; they were included in the trial from the 29th to the 43rd day after the onset of an infarction, and they comprised some who had and others who had not been treated with anticoagulants in the acute stage. Many complications excluded patients from the trial—for instance, malignant hypertension, valvular disease of the heart, a blood-urea of over 60 mg. per 100 ml.—but patients with cardiac arrhythmia, cardiac enlargement, and hypertensive heart-disease controlled by therapy were not necessarily excluded. Patients who could not attend regularly at a centre also had to be excluded. Because of these strict criteria two-thirds of the patients admitted to the participating centres with a diagnosis of myocardial infarction had to be excluded, and 383 patients were eventually studied. We are encouraged to find that the working party used the treatment and control methods that we have advocated as the most suitable at present available. The patients were divided into treated and control groups. The treated group were given the anticoagulant phenindione, and the dose was controlled by Quick's one-stage prothrombin-time test; enough of the drug was given to keep the prothrombin-time at 2–2$^1/_2$ times the normal figure. The control group were given identical tablets containing only 1 mg. of phenindione, and they attended regularly for clinical and laboratory tests; this was done so that the control should take account of possible psychological effects and the effect of traces of anticoagulant. Both groups of patients were seen regularly at intervals of 2–3 weeks, and patients were followed up to a maximum of 3 years after the original infarction. The treated and control groups were referred to as " high-dosage " and " low-dosage " groups respectively; and the patients were allotted to the two treatment regimes in a random manner, but in such a way as to ensure approximately equal numbers in the age-groups and the various clinical subdivisions. The tables show how well this was managed.

Three indices of effectiveness of the regimes were used: the death-rate from all causes, the frequency of myocardial reinfarction, and data about ability to return to work and the presence of angina or dyspnœa. The comparison between the two treatment groups showed definite differences. The death-rate was higher in the low-dosage men than in the high-dosage men; no such difference was found in the women, but the number studied was small. This difference in the death-rates was not quite significant, but " when infarcts serious enough to cause permanent withdrawal from the trial were added to deaths as a combined index of prophylactic failure there was a significant reduction in their frequency among males receiving the high doses, and there was a suggestion of a better result in males under the age of 55 ". The frequency of reinfarction was definitely lower in the treated men; under the age of 55, men on high doses had only one-fifth of the recurrence-rate of those on low dosage, and over the age of 55 the rate was halved in the high-dosage group. In the high-dosage group, too, more men returned to work and they were more commonly free from angina; the results as regards freedom from dyspnœa were not significant. On the other hand there were more hæmorrhagic complications in the high-dosage group: there were 4 major cerebrovascular accidents including 1 fatality, and 48 minor incidents, compared with 1 cerebrovascular accident and 8 minor incidents in the low-dosage group.

These results are in line with those reported by Manchester [10] in Washington, D.C., and Bjerkelund [11] in Norway, though the British results are more in keeping with the less favourable estimates of Bjerkelund. But in both Norwegian and British studies " the risk of death and cardiac failure or re-infarction is reduced significantly in younger males in the early stages of follow-up "—i.e., in the first few months after recovery from the actual infarct. The working party agree, too, that anticoagulant therapy can preserve the life of patients with serious cardiac damage by reducing the incidence of thrombo-embolic complications. And they consider that the method of selection and clinical grouping of their patients is likely to underestimate, rather than overestimate, the benefit of anticoagulant treatment.

This report will strengthen the public demand for anticoagulant treatment to be continued after recovery from myocardial infarction—if necessary for years. The working party did not pursue their investigations beyond 3 years, but we do not yet know how long treatment should be continued—whether it should be for the rest of life or for a limited period. Even if it is to be only for a period of, say, 3 years, hospitals everywhere will have to provide extra medical and technical staff, extra laboratory space, and extra record clerks to deal with a steadily increasing number of patients who will have to attend every 2–3 weeks. Unfortunately a postal service for delivering blood specimens at laboratories not less than 24 hours after withdrawal is not practicable in this country, where the post-office cannot guarantee delivery and shuts down at weekends. Hospitals must therefore try to estimate what is needed, and some have already got schemes under way. Similar clinics have been organised in the past for the control of diabetes mellitus and are now part of the hospital service; we hope that the Ministry of Health, boards of governors, and regional hospital boards will not put financial obstacles in the way of this clearly desirable addition to the hospital service. It will be much less expensive than some recent developments, such as cardiac surgery; and it can prolong the working life of a group of men at an age when they are often of greatest value to the community.

THE CASE FOR CASE-WORK

" *Nonne*—expecting the answer yes." The well-known Latin interrogative device, though perhaps implying some lack of faith in the respondent's tact or acumen, at least makes instantly clear the questioner's position. Mr. Huws Jones may well have regretted the lack of an English equivalent when he bravely asked the Institute of Almoners at their annual general meeting on March 20 " Is Our Social Worker Really Necessary ?" As it was, he hastily admitted that for those who had first-hand experience of what social workers did, it must be hard to take the question seriously. But he persisted in asking it, for he believed that both the profession and the people they were trying to help would gain from a detached appraisal of social work.

The answer might be self-evident, but to provide the evidence to support it would not be simple. Human beings and their reactions are not readily susceptible to measurement in terms of mathematical precision. Where there is almost infinite variety, and a plethora of

10. Manchester, B. *Ann. intern. Med.* 1947, **47**, 1202.
11. Bjerkelund, C. J. *Acta med. scand.* 1957, **158**, suppl. 330.

imponderables, it is difficult to find groups of rigidly comparable controls; where there is dire need, help cannot be refused to preserve the integrity of a series. Again, to many hard-pressed social workers the collection and analysis of evidence must not unnaturally seem unimportant and trivial beside the actual work itself. Mr. Huws Jones sympathised with the distrust, which social workers often shared with clinicians, of the scientists' " premeasured scales and sanctimonious precision ", but he thought it could be carried too far. Such small inquiries as had been held on, for example, juvenile employment and probation, had offered valuable directives for future work and for the economical deployment of our limited force of social workers. Apart from results, the organisation of an investigation usefully forced overbusy people to pause and define their aims and take stock of their methods. He believed in " better knowing for better doing " and some of the distrust, he hinted, might be founded in a reluctance to accept results which may be unexpected or occasionally painful.

Mr. Huws Jones firmly and realistically pointed out that social workers would more easily win the time, money, staff, and facilities which they need for their job if they could point to proof, simply presented, of the contribution they are making to the economy of the country—the number of workers who returned to their posts after a shorter spell in hospital, the number of young men on probation who did not return to prison, the number of school leavers who chose the right career. And indeed if social workers could offer evidence of this kind, the community, many of whom share their unjust suspicions of precise proof, would probably happily take on trust their intangible contribution to the country's welfare and happiness.

THE MECHANISM OF MIGRAINE

VASCULAR changes seem to contribute largely to the mechanism of migraine; many believe that constriction of arteries initiates an attack—with an aura of cerebral dysfunction if the affected vessels are cerebral—and that thereafter excessive vasodilation, perhaps accompanied by some change in vessel walls, accounts for the throbbing headache. The response to vasomotor drugs both in the aura and in the headache phase supports this hypothesis to some extent.

Assuming that there is vasodilatation, its immediate cause remains a problem. The occurrence in some patients during an attack of such signs as nasal congestion and lacrimation has suggested that parasympathetic overaction is a common factor. If this were so acetylcholine, as the chemical transmitter of parasympathetic impulses, might be present in abnormal quantity. Kunkle [1] has investigated this possibility. A group of 22 patients with migrainous headaches were separated on clinical grounds into those with involvement mainly of intracranial and mainly of extracranial arteries. The presence in cerebrospinal fluid, taken during an attack, of an acetylcholine-like substance was sought by a bioassay method. Such a substance was found in 5 of 9 " intracranial " headaches, and in none of 10 " extracranial ".

The criteria adopted in this work for a headache arising from intracranial arterial dilatation are not beyond criticism. Nevertheless, so far as it goes, the evidence supports the acetylcholine hypothesis. As Kunkle points out, this hypothesis could be readily confirmed if atropine could somehow be introduced locally to the vessels supposedly under the action of acetylcholine; but in man this is not easy. These findings, though they may provide us with further knowledge of the mechanism of migraine, suggest no answer to the equally interesting question of localisation—why the mechanism should operate almost exclusively on the vessels of the carotid tree, and often in a given individual constantly on the same small portion of that tree. Perhaps we shall have no answer to this until we learn more of ætiology—of what throws the migrainous mechanism into activity.

1. Kunkle, E. C. *Arch. Neurol. Psychiat.* 1959, **81**, 135.

FOR TEACHER AND FOR TAUGHT

IT is a sign of the maturing of an academic discipline when those who take part in it seek to define its limits and content. This process is taking place in general practice now, deriving impetus from the work of the College of General Practitioners, which has perhaps the least definable of all fields of medical endeavour.

Evidence of the ripening process is shown in two publications by the college designed to help new entrants to general practice whose previous experience has been largely theoretical, and also to help those responsible for guiding young men and women in trainee posts in general practice. It is interesting—and perhaps significant as showing the broad basis which gives the college its strength—that one of these publications comes from a faculty of the college, the other from the postgraduate education committee of the college itself.

Outlines of General Practice [1] is a real attempt to classify and set down in heading form the bewildering variety of responsibilities, duties, problems, and activities that form part of every day in practice but which are unknown to the houseman or the registrar. From the design of surgery premises to the abbreviations commonly used in note-taking, from the finance of medical practice to medical etiquette and ethics—the notes range widely; and each heading could be developed into a paragraph, each section into a chapter, by the senior experienced practitioner who has encountered each problem and found his own solution. The authors of this booklet, members of the Midland faculty of the college, have shown wisdom in restricting their brochure to headings many of which pose questions to which the newcomer to practice must learn the answers, either directly in locum appointments or from the senior colleague who may be his trainer. Each trainer would write the chapter a little differently, passing to his pupil a slightly different slice of the experience of his life. There are no fixed stereotyped methods in general practice, and it is as well that young men should not be taught to expect them.

The memorandum for the Guidance of Trainers,[2] produced by the postgraduate education committee of the college, is a smaller document, perhaps because it is assumed that the good general practitioner needs to be reminded of less. There is a full description of the best of surgery premises and equipment, with laboratory work on a scale beyond the range of those in practice, and a good account is given of the local-authority services, so many of which are duplicated by the practitioner's own welfare and antenatal clinics.

1. Outlines of General Practice. By A. J. LAIDLAW. College of General Practitioners: Midland Faculty. 2nd ed., pp. 69.
2. Memorandum for the Guidance of Trainers. Supplement to the *Journal of the College of General Practitioners*. February, 1959. Pp. 15. 1s.

There are, however, strange omissions; and it is surprising that neither volume gives adequate guidance to the trainer or the trainee on the structure and function of the service in which both will be at work—the National Health Service. True, the calculation of the Central Pool is explained, with the aspects of practice expenditure on which tax relief can be claimed; but nowhere is there a succinct account of the working of an executive council, or the composition of a local medical committee. These notes will be read by many who are not yet familiar with the pattern of National Health Service practice.

Another omission is any account of the relation of the practitioner to the hospital services with which he will be in everyday working contact. A useful set of guidance headings could be compiled for the future editions which will certainly be required. Patterns of practice change, new methods come in rendering old ones obsolete; and regular revisions of these brochures will enable family doctors to keep truly up to date. Trainers will come to expect this help from the college, and no doubt they will not be disappointed.

ARSENIC AGAIN

IN 1957 some 25% of the potato crop in Great Britain was sprayed with a mixture of sodium and potassium arsenite as a defoliant,[1] and the proportion sprayed was probably even greater last year. The widespread use of arsenic in this way dates from 1951–52 when there was a temporary world shortage of sulphuric acid, which had previously been used for the same purpose.[2] How great a risk to man and animals is involved in this change?

Apart from regulations on protective clothing of those who apply the spray and a ten-day interval between spraying and harvesting, there are no legal restrictions on the use of arsenic herbicides; in particular there is no obligation to fence off sprayed fields or to display warning notices. Whitehead [3] investigated four operators, all experienced in using toxic sprays, who had been spraying arsenite under supervision. One man complained of nausea and vomiting, and three were excreting an excessive amount of arsenic in the urine. These four were investigated again last year [4] when the urinary arsenic content was found to be little altered. But the risks extend beyond those handling the spray to potato pickers and to their children, who often accompany their parents to the fields, and perhaps even to the consumer. Picnics are usually eaten with unwashed hands; and blackberries covered with a fine mist of spray are a further danger. As regards consumers, the Ministry of Agriculture and Fisheries investigated the arsenic content of 450 samples of potato.[1] Only 2 samples contained more than the recommended limit of 1 part of arsenic per 1,000,000,[5] but the survey included an unspecified number of non-sprayed potatoes, both home-produced and imported. The Ministry [6] has also reminded farmers that cabbage plants should never be sprayed with arsenite—a dangerous practice that had been started in Kent.

Cattle may stray, or pasture may be contaminated by spray from a neighbouring field. Unfortunately, cattle are attracted by the distinctive odour of the spray: there are records [7] of electric fences being broken down to get at the sprayed haulms, and even of cattle eating soil from an area where spray had dropped off the fleece of sheep. Moreover arsenic is so poisonous that liquid spilt during the movement of spraying machinery across pasture has sometimes caused illness and even death. Some of the accidents are caused by farm-workers' ignorance of the high toxicity of arsenic compounds:

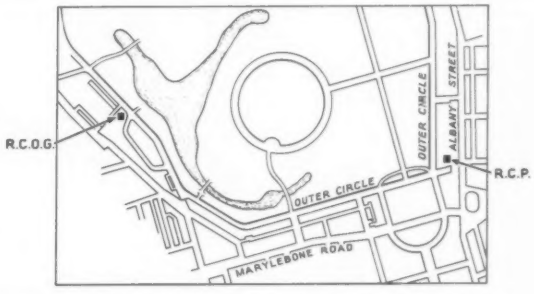
> "A herd of cattle wandered through a broken fence into a recently sprayed field. Five died within 4 hours and two more within 48 hours: analysis of the organs confirmed the diagnosis of arsenical poisoning." [7]

Parker [7] asks whether farmers would quite so readily use sodium arsenite if the tin containing it bore the information that a dressing for a 10-acre field, at 10 lb. per acre, was sufficient to kill 20,000 cattle, 140,000 sheep, or 640,000 pigs.

One encouraging feature has been the development of a non-toxic defoliant [8] which may replace arsenic as a spray, although it will be more expensive. Certainly we should not defer action until someone is accidentally killed from this cause. If arsenic cannot at once be replaced by a non-toxic herbicide, why should sulphuric acid not be used again? The drawbacks of sulphuric acid—greater cost ($1\frac{1}{2}d.$ per cwt. of potatoes), staining of clothes, and burning of skin—seem a small price to pay for stopping the use of arsenic.

COLLEGES IN REGENT'S PARK

OUR last issue contained an announcement that the Royal College of Physicians is to move to a site at the south-east corner of Regent's Park where Someries House now stands. The Crown Estate Commissioners explain [9] that, though the original building of Someries House was



designed by Nash, "as much again has been added to it, and the Gorell Committee recommended that it should be demolished". A start has been made on the plans for the new building, and work on the site can begin as soon as the Ministry of Works vacates Someries House in 1961. The Royal College of Physicians, on one side of the park, will "balance" (as the commissioners put it) the new building now being erected for the Royal College of Obstetricians and Gynæcologists on the opposite side, where Sussex Lodge formerly stood. This should be nearly ready by the end of this year.

Prof. ROBERT PLATT has been re-elected president of the Royal College of Physicians of London.

Dr. CHARLES HARRIS has been re-elected vice-chancellor of the University of London for 1959–60.

1. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 2.
2. *Lancet*, 1957, ii, 1047.
3. Whitehead, T. P. *ibid.* p. 953.
4. Whitehead, T. P. Personal Communication.
5. Food Standards Committee: Report on Arsenic. H.M. Stationery Office, 1955.
6. Ministry of Agriculture, Fisheries, and Food: Tech. 32/57.
7. Parker, W. H. *Agric. Rev., Lond.* August, 1958.
8. *Mon. Bull. Minist. Hlth Lab. Serv.* 1955, **18**, 1.
9. The Future of the Regent's Park Terraces. H.M. Stationery Office. 1959. Pp. 10. 9*d*.

Public Health

NEGLECTFUL MOTHERS

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THIS paper is a follow-up study of 100 mothers placed on probation and admitted to residential training homes after appearance before the magistrate's court for child neglect (Sheridan 1956). It describes the use they made of their training.

THE MOTHERS

The women were not a complete cross-section of mothers brought before the court for child neglect, for this type of probationary training was restricted to married women who had some sort of permanent dwelling of their own to which they could return, so that it was likely they would be able to put into practice what they had learned. 2 were recent widows. The age-range of the mothers was 17–46 years, with an average of 27½ years. The number of living children varied from 1 to 15. Their average intelligence quotient on the 1937 Terman-Merrill scale (form L.) was 79·8.

From the reports of probation officers, from discussions with the staff of the homes, and from personal interviews with the mothers, the general picture which emerged was of disordered existence from early childhood.

Almost without exception the women were members of large families. Their fathers were usually unskilled labourers, intermittently employed. Their mothers seem to have been incompetent and overwhelmed, but were often held in much affection. The girls' own history followed a familiar pattern of irregular school attendance, poor scholastic attainment, wayward adolescence, numerous dead-end jobs (many were cinema usherettes), early illegitimate pregnancy, and enforced marriage with an equally ignorant and irresponsible youth. There was usually evidence of affection between the young couple at the start and some attempt on the girl's part to cope with housekeeping and children during the first months or years of marriage; but as the size of family increased there were difficulties of all sorts—material, emotional, and financial—leading to all-round deterioration of domestic circumstances, more frequent quarrels between the marriage partners and with relations and neighbours, mounting debts, loss of interest in children and in personal appearance, and final inability to face the needs of daily existence. Extreme poverty was unusual. Very few were immoderate drinkers, but many were heavy smokers.

This general pattern was by no means constant and every woman had her own problems and contradictions. Some were gentle and stable, but incompetent. Others were intelligent and capable, but unpredictable in their behaviour. Not all girls brought up in maladjusted derelict families became neglectful mothers. Many of the siblings of the mothers were responsible parents and respectable citizens. The factors which render the girl particularly susceptible to breakdown seemed to be poor moral and material standards in early life, unstable personality, low mentality, ignorance, and ill health.

Before admission to the home every woman (and child) was medically examined by her family doctor, by a medical officer of the local authority, or, if she had been remanded in custody, by the prison medical officer. The examination was carried out primarily to exclude contagious disease, but also to provide information about her past medical history and present state of health. Certain clinical signs and symptoms repeated themselves with striking constancy.

The mothers were generally undersized, with pale expressionless faces, dragging feet, and drooping posture, giving an impression of complete physical and emotional exhaustion. Many presented a type of depression which seemed to partake of a moral apathy which was not culpable, of a mental withdrawal that was not schizophrenic, and a physical lethargy which was not mere sloth. A few were resentful, anxious, and aggressive. Their appearance was unkempt. Their personal habits, particularly in elimination and menstruation, were uncivilised. Their ignorance of child care was abysmal. They had incredibly little knowledge of cooking or cleaning or budgeting and still less of sewing, washing, ironing, or bedmaking. It was difficult to believe that any girls growing up in Britain today could remain so profoundly ignorant.

57 of the mothers came from urban districts and 43 from rural areas. The average age at marriage was 20 years 3 months. The average age at the birth of the first child was 1 year younger. 63 of the mothers admitted to premarital conception and this was probably an underestimate.

CHILDREN

The earliest age of first pregnancy was 15 years and the latest 27 years. 28 of the mothers had children before they were 18. Between them the mothers had produced 470 liveborn children of whom 48 had died, the majority before the age of 1 year. (The infant-mortality rate was thus about three times as high as the average for 1946–50.) At the time of their stay in the training home the whereabouts of their living 422 children was as follows:

With mother at training home	216 (all under 5 years)
In care of local authority	151 (between 5 and 15 years)
Working	15
Temporarily with relations	13
Permanently with relations	7
Mental-deficiency hospitals	5
Tuberculosis hospital	2
Approved school	2
Open-air school	1
Legally adopted	10

Thus of the 422 children 377 were in some form of public care, and some of those working or living temporarily with relations were subsidised by public funds.

The mothers had all been accused of child neglect, and not of cruelty. On admission few of the children showed signs of severe undernourishment, but most of them were malnourished in the sense that they had been wrongly fed. Except those whose health had benefited from placement in residential nurseries while their mothers were on remand in prison, they were underweight, fretful, pale, apathetic, and incontinent. I saw among them the worst cases of rickets I have met for many years. Most of them were functioning at a lower level than their potential capacity. They were suffering from maternal deprivation in every sense of the term.

A number of them would have been assessed as mentally defective on a single examination immediately before admission. Their rapid improvement had to be seen to be believed. After a few days of adequate food, warmth, rest, cleanliness, and fresh air, together with the more frequent handling, talking to, and playing with, which, often for the first time in their lives, their mothers had time and energy to give them, the children blossomed.

FATHERS

The fathers were not seen, but information was obtained from the case-records and from the mothers. Except for 3 or 4 elderly men, they were usually little older than

their wives. More than half of them had already been before the courts, usually for petty thieving, brawling, or child maintenance. In general they appeared to be immature, irresponsible, wayward, quarrelsome, and irregularly employed.

Of the 98 living husbands, 65 were jointly charged with their wives before the court (31 being sent to prison, 29 placed on probation, and 5 fined), 27 were absent, and 6, who were at home, were considered blameless. This last small group was particularly interesting. Though most of the wives' social failure seemed to be at least partly due to the husbands' deficiencies, these 6 men had made valiant efforts to keep their homes together, to buttress their wives, and care for their children. In the absentee group there were 10 who were considered to be satisfactory husbands, but 9 failed to contribute adequately to the upkeep of their families. 8 who were in hospital were unable to contribute. From all the evidence available, 32 of the 98 living husbands appeared to be, in their way, satisfactory husbands and fathers, although at least half of them must be designated unsatisfactory citizens. The stability of the father proved to be an outstanding factor in the outcome of the mother's training.

While the mothers were in the home, the fathers were encouraged to keep in touch with their wives by letters, telephone calls, and visits. The training-home staff, probation officers, and child-care officers made every effort to improve relations, to soften resentment, to patch quarrels, and to stimulate interest in the children's progress. They encouraged the husband to improve the material equipment of the home.

Results of Training

The usual period of probation was two years with "a requirement to reside" in the training home for four months. Thus the probation officers were under obligation to supervise the mother for at least twenty months after her return home. Many continued to visit for much longer. The organisations responsible for the homes also tried to keep in friendly touch with the mothers and I read many notes of interviews and dozens of letters from women who looked back to their training and to the staff with gratitude and affection. The information thus collected, although valuable in detail, was difficult to classify, and I was allowed to circulate a detailed questionnaire to the probation officers asking for up-to-date information about the mothers' progress and, where possible, for a classification on all items in four categories—very good, good, fair, and poor.

Mothers

95 mothers had already completed their term of probation; the earliest mothers included in the survey had been home nearly seven years. Of the remaining 5, 3 had left the home eighteen months before, and the 2 last fifteen months before. The final classification was usually indicated six months after return from the training home and by twelve months was usually certain.

Of those who were ultimately classed as failures, most had made some feeble effort to improve their standards for a few weeks or months after leaving the training home, and then regressed. The 3 most dramatic failures were psychopathic young women of good intelligence who seemed to benefit greatly from their training, while in the home, but crashed very quickly once the support of its kindly but firm discipline was withdrawn.

At the end of the period of review, 75 women were judged to have benefited from their training, while 24 were classified as failures. 1 died in the final weeks of training. The others were grouped as follows:

Group		*No. of women*
A	(Outstandingly successful) ..	14
B	(Progressing satisfactorily) ..	25
C	(Improved, but still need help)	36
D	(Failed)	24 (including 1 suicide)

To discover, if possible, the common factor which made for success or failure, the case-notes of the 14 outstanding successes and the 24 failures were further examined.

Contrary to expectations, though not to experience as the work progressed, the mother's *intelligence quotient* was not a significant factor:

	Group A	*Group D*	*Whole series*
I.Q.	78·2	79·2	79·8

Nor was the mother's *age on admission*, though there was a tendency for success to be associated with slightly older age:

	Group A	*Group D*	*Whole series*
Age	31·3 years	28·6 years	27·5 years

Although the numbers are small, the difference in *premarital conceptions* perhaps indicate the more stable character of the successful mothers.

	Group A	*Group D*	*Whole series*
Premarital conception	6 (*43*%)	17 (*71*%)	63 (*63*%)

The average *number of children* in the family showed little difference:

	Group A	*Group D*	*Whole series*
Children	4·6	4·4	4·2

Unexpectedly *rural or urban residence* seemed to make a considerable difference, but again the numbers are small:

	Group A	*Group D*	*Whole series*
Urban	10 (*71*%)	10 (*41*%)	57 (*57*%)
Rural	4 (*29*%)	14 (*59*%)	43 (*43*%)

Since this cannot depend on any substantial difference in probation supervision, it may perhaps reflect the more concentrated public-health and welfare facilities in the cities. The example set by a large number of neighbours with somewhat higher standards of housekeeping and child care, and perhaps their willingness to lend a helping hand, may not be without effect.

The *health of the mother* at the end of the period of review was a highly significant factor:

Health	*Group A*	*Group D*
Very good	3	1
Good	10 (*92*%)	7 (*33*%)
Fair	1 (arthritis)	7
Poor	..	8 (including 4 in mental hospitals and 1 suicide)

The most important factor of all was a steady and affectionate *husband*. So far as the mothers in this study were concerned, it was preferable to be without a husband than to be tied to an unsatisfactory one.

Group A		*Group D*	
Satisfactory husband	11	Satisfactory husband	1
Absent husband		Fair but weak husband	2
Sanatorium	1	Unsatisfactory husband	18 (3 in prison)
Absconded	1 (3)	Absent husband	
Dead	1	Hospital (multiple sclerosis)	1
		Working away ..	1 (3)
		Mentally ill ..	1

Of the 6 husbands originally classed as "blameless" 3 were husbands of group-A mothers. The fourth was the husband of the woman who died while training. The fifth was the husband of a group-B mother. The sixth was husband of a group-D mother. He had made commendable efforts to keep his family intact, but was eventually obliged to leave his wife, who appeared to be incorrigible. When last heard of she was in prison. The group-D wife whose husband was working away was also serving a prison sentence, for manslaughter of her second child.

At the end of the review all but 5 of the marriages of the 24 mothers who failed to respond to training (including the woman who committed suicide) were broken. The mothers themselves were scattered as follows:

Separated and evicted	8
Prison	4
Mental hospital	4
Absconded	2
Suicide	1
Still (precariously) with husband	5

Children

At the time of their training the 14 group-A mothers had 65 children. At the end of the period of review this number had increased to 80. No child had died. All these mothers were living in their own homes. Of their 80 children, 76 (including a few who were working) were at home and 4 were in public care. These 4 were children of a woman of low intelligence who had 9 children including 2 sets of twins. She was a stable, devoted mother and the family was a happy and united one, but as it was felt that she could not cope with so many young children, these 4 had been taken into care near home where the parents and siblings visited them often.

The 24 group-D mothers between them had 105 children on their admission to the training home. At the end of the period of review the number had increased to 113. The whereabouts of these children was as follows:

Still with one or other parent	15
Working (usually away from home)	9
With grandmother	2
Dead	2
In public care	85

DULL MOTHERS AND INTELLIGENT MOTHERS

10 of the mothers had I.Q.s under 60 and 8 had I.Q.s over 110 (3 were over 120). It seemed worth while to examine these records more closely.

WOMEN WITH LOW INTELLIGENCE

Group A

I.Q. 48—Blameless husband. Stable woman. Happy marriage. 9 children (4 in care).

Group B

I.Q. 46—Satisfactory husband. Stable woman. Children at home.

I.Q. 46—Gypsies. Devoted family. Children at home.

I.Q. 57—Satisfactory husband. Stable woman. Children at home.

Group C

I.Q. 48—Husband in mental-deficiency hospital. Stable woman. 2 of 4 children in care.

I.Q. 53—Husband mentally very dull, but steady. Stable woman. Children at home.

I.Q. 58—Husband mentally retarded, but steady. Stable woman. Children at home.

Group D

I.Q. 52—Husband in prison. Unstable woman. 6 children in care and 1 in approved school.

I.Q. 55—Broken marriage. Husband unsatisfactory. Unstable woman. Children in care.

I.Q. 59—Husband in prison. Woman in mental-deficiency hospital. Children in care.

It would seem that mental backwardness is not a bar to rehabilitation, provided the woman is stable and has a satisfactory husband. When low intelligence is associated with instability the prognosis is very poor.

WOMEN WITH HIGH INTELLIGENCE

Group A

I.Q. 118—Very young. Reared by overindulgent grandmother. Previously wayward, now stable. Steady husband. Children with parents.

Group B

I.Q. 123—Enforced unhappy marriage at 16. Husband now in mental hospital. Children with mother.

Group C

I.Q. 124—Very unstable. Husband also unstable. Elder boy in home for maladjusted. Other children at home.

Group D

I.Q. 111—Unstable woman. Weak husband. Precarious marriage. Children in and out of care.

I.Q. 112—"Melancholy, unstable and irresponsible." Husband psychotic. Children in care.

I.Q. 114—Very unstable. Now in prison for manslaughter of new baby. Satisfactory husband. Elder child with grandmother.

I.Q. 118—Incorrigible psychopath. Unsatisfactory husband. Absconded and abandoned children, who are all in care.

I.Q. 127—An incorrigible psychopath. Weak husband. Marriage broken. Children in care.

These brief histories speak for themselves. It would appear that when a woman of high intelligence comes before the court for child neglect, she is likely to present a serious problem in rehabilitation.

Discussion

These bare figures can give little idea of the sum of human wretchedness they cover. Whatever their deficiencies of omission and commission, these women, when one comes to know them, cannot fail to arouse compassion and concern for their future and their children's future. The case-files bear witness that all who deal with them feel the need to look beyond the shocking facts to the puzzling woman beneath—the magistrate, "She needs training, not punishment"; the probation officer, "Backward and slow, but not vicious by nature: she lost heart"; the family doctor, "I have known this woman since she was a little girl: she is not bad really: she needs help"; the prison doctor, "Very pale: slept like a log on arrival"; the warden, "She sat for several days staring before her". Sometimes a few words highlighted the extent of our own ignorance. A mother kept repeating to me in a dazed fashion: "They came and took all my children away in a van. Like they were going to their graves. I felt it dreadful". A nursery assistant, pointing out two little brothers aged $2\frac{1}{2}$ and $3\frac{1}{2}$ whose mother had been remanded to prison, said "D. always clings tightly to M.'s hand like that wherever he goes. He is terrified of being separated from him". Discussing the mothers' partiality for children's comics, the warden remarked: "But what they like best of all are girls' school stories". The children's officer expressed more than her own bewilderment when describing how a 20-month-old baby welcomed home from prison the father convicted of wilfully neglecting him. "He just threw himself at the man with a yelp of joy".

Child neglect is only one symptom of a severe family disease of complex ætiology. Where there are so many imponderables, prognosis can never be certain. But this study, though far from complete, has at least shown that a large proportion of neglectful mothers will benefit from understanding treatment, and has underlined the importance in rehabilitation of the steadiness of the husband and the good health and mental stability of the mother. It may also suggest the importance of the accessibility of public-health and social services and the influence of neighbours.

The aim must not only be to diagnose and treat this degenerative family disease, but first and foremost to prevent it. It is generally agreed that committal to prison is not a constructive solution. As an alternative, the training homes have much to commend them. They provide good food, rest, regular hours, relief from anxiety, and the support of kindly discipline. They give a practical train-

ing which is repeated day after day at a level that the mother can understand, so that good habits of home-making and child care may be established as firmly as the four-month stay allows. The main drawback of this training is that it dislocates family life and that it cannot include the father. Though a short spell of relief from a situation which has become intolerable is of considerable benefit to the mother, any long separation from husband and children should be avoided. Treatment, if it is to be truly effective, must be applied to the family as a whole. It should be carried out at home on informal, practical lines, using wherever possible the ordinary services of the community, so that the mothers do not feel marked out among their neighbours.

In the present state of our knowledge it seems that a proportion of neglectful parents must be classed as incurable, owing to gross deficiencies in one or other of them, the mother being the more important because her care is more necessary to the child. Earlier recognition of these families should be possible. Mental instability and social maladjustment of this degree seldom develop suddenly in adult life. The indications of future trouble should be discernible in boys and girls before they become adults, indeed before they leave school. The educational implications are obvious. It would also seem advisable to devise some means of following up these children " at risk " through their adolescence, so that, while respecting their rights and privacies, they may be given help and guidance before it is too late.

I am grateful to the Home Office for permission to publish this report of an investigation mainly carried out when I was a member of the medical staff of the Children's Department Inspectorate. The views expressed are my own and do not necessarily reflect official opinion.

The study, spreading as it has done over ten years, would not have been possible without the help of the probation officers who completed the 100 questionnaires and of the staffs of the two homes. It is impossible to thank them all, but I wish particularly to thank Brigadier Gladys Newcombe, of the Salvation Army, Mayflower Home, Plymouth, and to Miss Julie Haw and her successor Miss Howland of the Elizabeth Fry Memorial Home at Spofforth Hall, Yorkshire.

REFERENCE

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Ice-cream Regulations

On April 27 new regulations relating to ice-cream,[1] based on recommendations of the Food Standards Committee, will come into operation in England and Wales. The main changes made by the regulations will be as follows:

1. That standards are to be fixed for dairy ice-cream and for milk ice, which are required to contain milk fat and must not contain any other fat.
2. That saccharin and other artificial sweeteners are not to be used in any ice-cream or in milk ice, and no minimum sugar content is laid down.
3. That ice-cream made with non-milk fat is not to be labelled or advertised in a way which is suggestive of butter, cream, or milk; but such ice-cream may continue to be sold as " ice-cream ", and it may bear a statement that it contains skimmed milk solids.
4. That after Nov. 30 all prepacked ice-cream which is made with non-milk fat must be labelled that it contains vegetable or non-milk fat if it is sold as " ice-cream ".

The present requirements that ice-cream must contain not less than 5% fat and not less than 7·5% milk-solids-not-fat are included in the new regulations and so continue in force. The new regulations will revoke and replace the existing Food Standards (Ice-Cream) Order, 1953.

The Secretary of State for Scotland proposes to make corresponding regulations which will apply in Scotland.

1. Food Standards (Ice-Cream) Regulations, 1959, no. 472; Labelling of Food (Amendment) Regulations, 1959, no. 471.

The Wider World

HOSPITAL MEDICINE IN RUSSIA

J. B. HARMAN
M.D. Cantab., F.R.C.P., F.R.C.S.

LAST autumn I paid a 17-day visit to hospitals in Moscow and Leningrad. My first object was the usual one that tempts doctors to travel—the hope of finding different ideas, techniques, or points of view. What I wished to explore was hospital medicine at its best, with special attention to anything new that might be coming on from research.

It must be admitted that the prospects were not very hopeful. Before the Revolution, Russian medicine hardly existed except for a few outstanding individuals. Since then the first priority has been in public health, in epidemic control, and in training and distributing doctors. In any rational plan, the sort of medicine that I am interested in would be the last to be developed unless it was to be used for prestige, like a sputnik. Nevertheless, I did hope that there might be interesting differences, whether due to isolation, a conscious break with the past, or to the ferment of ideas that accompanies revolutions.

My second object was to find out whether a doctor could pay a professional visit to Russia, and be received, if he were neither invited, nor a member of a congress, nor a delegate of some sympathetic organisation.

* * *

The short answer to this second question is that it was possible. I wrote directly to the Minister of Health in Moscow, stating my plans, and was put in touch with the official who deals with foreigners. Towards the end of this correspondence I was left in some doubt as to what if anything would be done; but these doubts were cleared up through the good offices of the Foreign Office.

I was shown what I needed to see. The dozen institutions which I visited included a new district hospital, an old-established town hospital comparable in status to our upgraded county-council hospitals (taking students and with research staff), university hospitals comparable to a teaching hospital here, and institutes of hæmatology, neuropsychiatry, internal medicine, cancer, and endocrinology. These institutes are comparable with Queen's Square, the Royal Marsden, the Maudsley and so on. But their development and emphasis are different. They are nearly all new and were started primarily as research institutions. Each has a small hospital attached to it and they have a close liaison with similar organisations in all the republics of the Union.

Each visit lasted three to four hours. I and my Intourist guide would be received very punctually by the director in a spacious Edwardian office, and we would jockey for language. The elder doctors could speak German and did so. Some spoke English and always with an excellent accent. Mostly it was Russian through the interpreter, with frequent direct communication over her head in English or German by either party. French was useless. The director would then summon the other professors (this word denotes an academic grade, not a chair) and with half a dozen or so sitting round I would explain myself. Usually I found it helpful to suggest a clinical round or a visit to laboratories, as this raised points for discussion. We would then go back to the office and tie up loose ends.

Since I was a self-invited tourist, unknown to my hosts, and announced only a few days before the visit, there was

no call and indeed no opportunity to arrange any special demonstration. We chatted as colleagues, discussing the cases, the value of present methods and the hopes of new. Despite the difficulties of language and the nuisance of a visitor upsetting the day's work, there was seldom any failure of communication on these matters. Most of the doctors seemed anxious to show their work. One distinguished Academician expounded his interesting and stimulating views in rapid English for over 3 hours.

In my letter to the Minister I had offered to give a few lectures. One was arranged and given to an audience of about two hundred members of a psychiatric society.

The subject was a criticism of psychosomatic medicine as talked about and practised on this side of the Curtain. It would have aroused considerable opposition if given to a similar meeting here, and it did the same there, but for different reasons. In their opinion, our own orthodox views are so wrong as to be hardly worth criticising, and there was a certain sense of outrage that anyone should so much as discuss the subject without considering the tenets of the Pavlovian school. This omission was remedied by subsequent speakers, but they did at the end ask for a copy for publication.

I made a few inquiries about the possibility of our own postgraduates working for a few months in their clinics and research institutions. From the professional end this would present no difficulties, and they would be ready to do anything they could—but it would have to be arranged officially. This was confirmed at the Ministry, where I was told that foreigners could be taken only on an exchange basis, arranged through the British Council, or preferably the World Health Organisation.

* * *

The opportunities, then, of looking round were as good as anyone could reasonably expect. What was there to be seen? At this point one becomes very conscious of the difficulty of coming to correct and useful conclusions after so short a visit. This difficulty besets observers everywhere, but two things are liable to exaggerate errors in visiting Russia. The first is that intercommunication on this level is so recent and slight that one observer's opinions constitute much too large a proportion of our total knowledge to be safe. (This does not arise in respect of the States or Germany, for example, where any personal errors are corrected by an already vast body of knowledge.) The second is that Russia for us is not emotionally neutral, and this clouds judgment. Obviously I cannot claim a special immunity from this bias; but if it exists it could not play a large part in the judgment of what I went to see. I did not go with any intention of judging Russian medicine and comparing it with ours. I went simply to look for something helpful that could be used at home.

My impression of their medicine was of good sound stuff from the latest textbooks. The cases dealt with were the same as those seen in equivalent hospitals in this country—degenerative vascular disease, acute respiratory and urinary infections, thyrotoxicosis, mitral stenosis, peptic ulcers, chronic bronchitis, and so on. On these cases they make the same diagnoses and in the same way as here. They use the same drugs and for the same reasons. They performed the usual investigations and were trying what was newer—e.g., serum-transaminase. A little harmless nonsense existed, such as dry cupping to prevent pneumonia, bromide given intravenously, inhalations of garlic for bronchiectasis, and a high regard for spa treatments—all of which I took to be relics of Continental medicine in the '20s.

I saw no patients in Russian hospitals who would not have been admitted to hospital here. With the exception of cancers, I saw no forms of disease that are not common here.

The institutes have great opportunities of collecting special cases from the whole of the Soviet Union. Thus there were 200 cases of Cushing's syndrome on the books of the endocrine institute and 18 were in the wards when I visited. The cases in the oncological institute reflected the wide epidemiological differences in cancer throughout the country. The hæmatological institutes dealt almost exclusively with the reticuloses.

The routine laboratories were small and decentralised to each firm. Apparatus for electrocardiography, electroencephalography, and diagnostic radiography were there, but somewhat old-fashioned; X-ray therapy appeared to be very limited. Clearly Government bounty had not extended to the hospitals.

The impression was of medicine from textbooks rather than periodicals, because their introduction of such new things as antibiotics, corticosteroids, and radioactive isotopes is delayed. This delay is not because they are unaware of them. Although we on our side have only recently shown an interest in Soviet literature, they have been completely familiar with ours for many years. All important articles are translated, abstracted, and widely distributed. The delay is due to their having to await publication, to learn techniques from descriptions rather than example, and to wait for their own industry to produce the drugs. In this field they are in fact copyists—just as we all are to some extent. But, so far as I know, their copying is unrelieved by any occasion where they themselves have discovered something of importance and have therefore been first in its use. To the Americans, who originate and have first trial of many more things than we do, they would seem even more behindhand.

The Russians share the common medicine of Western civilisation. But so do the Americans, the Swiss, the Spaniards, and ourselves; and each of us makes something different out of it. What struck me about medical Russia was the Englishness of it all.

Practice was the same as in any good English hospital, and to me it was good, stable, sympathetic orthodox medicine, erring a bit on the side of timidity. There was nothing of importance I could disagree with, and nothing strange. No doubt their patients are underinvestigated by American standards, and many Continental physicians might think them undertreated. They were certainly not lured into overinvestigation by an abundance of medical apparatus and the fascination of gadgetry, but they had quite enough to misuse if they had been so inclined. Doctors have always found it possible to overtreat their patients, whether they possessed useful remedies or not. On the other hand the Russians are not, in this field, subject to the temptations inevitable when highly competitive commercial medicine is practised on a sophisticated populace.

This impression surprised me very much. It may have been wrong but it was certainly based on what I saw and not on preconceived notions.

* * *

The obverse of good sound medicine is often the absence of original ideas. In the clinical field I hardly met a single new idea—good, bad, provocative, ingenious, fantastic, or even silly. Except in psychiatry, it was all so orthodox and accepted with no hint of search, criticism, or enthusiasm. It may be that the difficulties of language and the circumstances of the visit were not propitious for this sort of exchange, or they may been too secretive to tell me. But I do not think this is the answer. They were proud of what they were doing and anxious to show it.

I was also surprised that so few attempts were made to extract information from me. It is true that they were

being asked to impart information and they did it with courtesy. Also they had no particular reason to think that I had anything to contribute. Nevertheless I cannot help feeling that more attempts would have been made to pump a foreigner visiting a dozen equivalent institutions in this country.

* * *

The exception to this sameness is psychiatry and psychosomatic medicine. These subjects are always deeply tinged with parareligious faith, and it was refreshing and stimulating to see another one. Their own dogmas are as rigid as ours, but different. Freud's views are anathema, being "idealist"—that is to say, his concepts cannot be described in terms of physiology. Sex is deemed to play little part in psychopathology, as in anything but the basic necessities in this puritanical and emancipated country. Heredity is muted, for the accent in a revolutionary world is on the changeable environment rather than on the same old types who had proved so unsatisfactory before. On the other hand, they have in Pavlov's work a materialistic approach which admirably fits their ideological demands. The work of Pavlov has been continued in physiology by Professor Bykov and others and applied to experimental and psychosomatic medicine by Academician Spiranski.

Western psychosomatics is a large and vague territory and includes much wisdom that has been known to physicians for centuries. The essential modern feature may be stated briefly thus. Emotions alter the function of various organs and thereby lead to gross permanent pathological changes in them: the corollary is that the management of these diseases should be through the adjustment of the emotions, which in effect means psychotherapy.

The Russian emphasis is somewhat different and arose from observation of the widespread changes in organ function that occurred during cortical stimulation and inhibition. The conditioned dog is still the basis of experimental preparation. In its present form the work is concerned with the central regulation of all the peripheral organs, and of their effect, in turn, on the cerebrum. At the lower level of function it is a synthesis of analytical physiology; at the higher level it goes some way in the study of higher cerebral activity but not nearly so far as Freud and his disciples.

This method is well adapted to study the interrelations of mind and body in health and disease; and to shed some light on the organic mechanisms of psychiatry. No particular therapeutic methods are implied; but the control system could conceivably be altered at any point in the circle of nervous communication—at the motor as well as at the sensory feedback. Alteration of cerebral mechanisms by organic means is not excluded. Psychotherapy by verbal methods is also practised, the basis being some attempt at reconditioning though it is not easy for an observer to know exactly what goes on.

This task, if I have summarised it correctly, is nothing less than the study of the integration of the whole organism. It is a matter of such complexity that research is more likely to yield gradual understanding than quick cures.

So far as practice is concerned they do much the same as we do, though they may offer different reasons for doing it. A good deal is just loose talk in terms of Pavlov, just as ours is loose talk in terms of Freud. They employ insulin treatment extensively. Electroconvulsion therapy was used, but sparingly they said. Leucotomy is forbidden. Sedative and stimulant drugs have the same place as here, but there was considerable use of their electro-sleep machine.

* * *

I conclude, then, that Russian internal medicine is a faithful copy of our own, and I see no point in thinking of Russia as a place of medical pilgrimage. Exceptions naturally must be made for the occasional outstanding individual, and also for psychiatry, which is always greatly influenced by the prevailing culture.

This, however, is not the end of the matter. The question arises whether the Russians will in the near future reach a state in which their work in this kind of medicine will have to be taken into account. It is obvious that conditions in Russia are changing fast, and also that they are a people fully capable of holding their own in science. In a centrally directed State the direction of effort is determined almost entirely by an assessment of priorities. Up till now internal medicine has had a low priority and there is still no indication, from outlay of money, that it has risen higher. This must affect the prestige of the profession and the quality of recruits to it. Today, many of the professors are elderly. They started in the pure European tradition, but their whole professional life has been spent in times of turmoil. The middle-aged group started in turmoil and to some extent their selection and training must have been affected by the revolutionary experiments. Things are now more settled and the basic tasks of the economy are completed, but I do not know whether this has encouraged enough recruits of the right calibre to compete in international medicine. If it has, probably at least ten years must pass before they contribute significantly. If not we can forget about the subject for the foreseeable future.

I am grateful to the governors of St. Thomas's Hospital and the Royal Marsden Hospital for financial help.

Dialogues of Today

AGE, ANGER, AND AXOLOTLS

SOCRATES: I hear, Eryximachus, that there are many critics in medicine today. Are they the angry young men?

ERYXIMACHUS: Not all critics are young, Socrates, but there are angry young men in medicine, and I have brought one of them with me today—my young colleague Enthusiasticus.

SOCRATES: Welcome, Enthusiasticus, and forgive my surprise when Eryximachus described you as young, for you seem already to have lost some of your hair in the service of your profession.

ENTHUSIASTICUS: I am only thirty-seven, Socrates.

SOCRATES: And as Eryximachus calls you his colleague, you are a consultant, I suppose?

ENTHUSIASTICUS: Alas, no, not yet; but I hope soon to become one.

SOCRATES: How old were you when you began to learn medicine?

ENTHUSIASTICUS: Seventeen.

SOCRATES: So after twenty years you have still not attained your goal. But I am told that in the higher mammals the length of gestation is roughly proportional to the duration of life, so I suppose you will have many more years to work as a consultant.

ENTHUSIASTICUS: Oh, no; I shall be too old to work when I am sixty-five.

SOCRATES: Then, like some insects, you spend a long time in immaturity compared with your stage of full development. And is there not some creature which never attains maturity at all?

ENTHUSIASTICUS: You are thinking of the axolotl, Socrates, which ends its life as a larva.

SOCRATES: And are there axolotls in medicine, too?

ENTHUSIASTICUS: Unfortunately, many; and registrars of my age are kept awake at night by the fear that they may end up as axolotls.

SOCRATES: If it is ever right to be angry it would seem to be

so in your case, Enthusiasticus. But are there other things, too, about which you are critical?

ENTHUSIASTICUS: Well, yes, Socrates. Things are changing so fast in medicine that it is only the young who can keep wholly up to date.

ERYXIMACHUS: Come, come, Enthusiasticus! Surely you must admit that the great advances in medicine and surgery are often made by men who are in the fifties. How, then, can it be only the younger ones who are up to date?

ENTHUSIASTICUS: Of course, what you say is true, Eryximachus, but that is just my point. For the specialists are all so busy making and keeping up with advances in their own specialties that they cannot know what is happening in all the other specialties too; and in any case the older you get the more difficult it becomes to alter your basic ideas and acquire new ones. So it is only the young, who have been educated in medicine during the past twenty years, who can see it as a whole, and be really up to date. Without them the work of our hospitals would fall to pieces. And yet they have virtually no influence upon the organisation of medicine and little upon medical education although they do much teaching. This is a state of affairs which has never occurred before, and for that reason the old do not recognise it.

SOCRATES: I gathered from Eryximachus that the old are sometimes angry, too. What makes them angry?

ENTHUSIASTICUS: Well, Socrates, the young are angry out of a sense of frustration. I do not think they often blame anybody. But the old seem usually to be angry with each other.

APOLLODORUS: It seems to me, Socrates, that when one is young it is natural to blame one's elders, whom one holds responsible for things as one finds them. But when one is old one has no-one to blame for the state of affairs but oneself and one's contemporaries; so it is natural to blame one's contemporaries.

SOCRATES: It would appear, then, that men are no more reasonable in their criticisms than in anything else they do. Why, then, do people take the criticism of the old so seriously?

APOLLODORUS: I can tell you one reason, Socrates. In former days a man had to stand up in the market-place or in the assembly of the people and utter his criticisms, and all men could see his face and hear his voice. And if he was embittered and angry without cause it was apparent to all, and his words were disregarded. But now the angry man expresses his criticisms in print, and is never himself seen, so that to the thousands who do not know him his words appear inspired by reason and not, as they often are, by feelings not wholly related to the subject.

SOCRATES: But is it not a good thing that all new ideas should be subjected to all possible criticism, and if they are sound will they not survive it?

ENTHUSIASTICUS: May I speak again, Socrates, for there is something which Apollodorus has not said about the older critics?

SOCRATES: The young will always have the last word, Enthusiasticus!

ENTHUSIASTICUS: It seems to me that to solve our problems is very difficult, and, as I have said, the older you get the harder it is even to understand them. That is why criticism by the old is usually destructive. But I would not mind that if there were more ideas for them to criticise.

Special Articles

PSYCHIATRY AND LOCAL AUTHORITIES

"THE good of the patient and of the community requires that the services of hospital, local authority and family doctor should be integrated as much as possible." To meet this need for integration the Royal Medico-Psychological Association and the Society of Medical Officers of Health make some joint recommendations.[1]

There is advantage, they say, in cross-representation on council, committee, and board. The M.O.H., for instance, should be able to join in the discussions of the hospital management committee, and the hospital psychiatrist in those of the local authority's mental-health committee. The regional psychiatrist should take a full part in planning the joint services for the community. Where no regional psychiatrist is appointed, this work should be done by a psychiatric advisory committee.

Ideally, consultation and collaboration should take place spontaneously—"not because of a system or machinery, but because all concerned know each other, have worked together, and understand each other's methods and problems". To this end it is strongly recommended that new entrants to the public-health service should be allowed to have part-time experience (about 150 hours in twelve months) in the three main branches of psychiatry—i.e., child psychiatry, mental illness, and the subnormalities. The trainee psychiatrist or registrar should similarly be seconded so that he may learn something of the problems and methods of appropriate departments of the public-health services.

In each area the actual form of the cooperative enterprise must be worked out to suit local conditions. It cannot be imposed by a regional hospital board, hospital management committee, or local authority, but these bodies can give valuable and necessary help and support.

Patients not resident in hospital should come under the care of an integrated service working from a special centre. This could be the centre for diagnostic and therapeutic services, including the screening of new patients according to their individual needs for appropriate treatment. It could also be the centre for a day hospital, patients' clubs, and so on. The psychiatrist and his staff from the hospital service should give all possible help and advice to the family doctor and to the local authority's staff and should do the psychiatric clinical work. The social workers of various categories should pool their efforts as far as possible in each area, working closely with and for both the M.O.H. and the hospital, and making contact with the related organisations. "The tendency should be towards the main provision of social workers being by the local authority so that the individual patient has continuous personal contact with the one worker. In some cases it might be satisfactory that they should be appointed jointly".

If the psychiatric hospitals are to undertake more teaching and make a full contribution to the mental-health service in the community, some increase in their senior staff will be necessary; but possibly the cost would be recovered through the resulting reduction in admissions to hospital beds. "It would be most undesirable for doctors to give these extra services at the sacrifice of their hospital patients or of their own free time."

The social worker with adequate training is essential to any scheme. The fully trained psychiatric social worker is regarded as necessary for child psychiatry and for senior positions elsewhere; "but there will never be enough to cover all the social work required, nor will it be necessary to employ them throughout the whole field. Others, such as mental-health workers, mental-welfare officers, and health visitors, have proved very valuable and can be increasingly useful if their training is properly developed." A social worker in mental health should be employed only under expert medical staff, to avoid being placed in a position for which he or she is not equipped.

Schemes of collaboration have been comparatively easy to achieve where the catchment area of the hospital is closely similar to the domain of the local authority. In some other places it may be necessary to adjust the catchment area.

1. Drafted by a joint committee whose members were: for the Society, Dr. H. M. Cohen, Dr. Rachel Fidler, Dr. J. A. Fraser, Dr. W. G. Harding, Dr. J. T. Chalmers Keddie, Dr. J. D. Kershaw, and Dr. J. A. Scott; for the Association, Dr. N. H. M. Burke, Dr. Mary Capes, Dr. N. G. Harris, Dr. J. V. Morris, Dr. T. P. Rees, Dr. F. H. Taylor, and Dr. D. H. H. Thomas.

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Medicine and the Law

Gas-gangrene following Fracture

A BOY aged 6 was taken to Raigmore Hospital, Inverness, having fractured his left forearm by falling from a gate, sustaining also a small wound on the inner forearm. He was treated for a simple fracture and discharged on the following day. Two days later he was readmitted, gas-gangrene having set in, and the arm had to be amputated at the shoulder. By his father he claimed damages against a woman house-surgeon in the orthopædic department and against the Inverness Hospitals Board of Management for alleged negligence in the treatment.

There were two orthopædic units at the hospital, each with a consultant surgeon and a house-surgeon, and, in addition, on the staff of the orthopædic department a senior registrar, whose duties included supervising the house-surgeons and directing the day-to-day treatment of patients. On the material dates—July 2 and 3, 1953—the registrar was on leave, and under the system in force his duties devolved on the consultants, so that the consultant in orthopædic surgery was acting as senior registrar for his own unit. When the boy was admitted to the hospital on the afternoon of July 2, the woman house-surgeon was acting under the supervision of the consultant.

The LORD ORDINARY found that what then happened was as follows:

1. The house-surgeon told the consultant that she had two small boys in the other room, that both had fractures in their arms, and that one had a little wound in the skin. Later, being worried about the wound, she asked what to do in regard to it.

2. The consultant's diagnosis was a greenstick fracture of both bones of the forearm; and he noted a minute wound (which he afterwards described as too insignificant to require excision) on the front of the forearm at the level of the fracture of the ulna. He regarded the fracture as "potentially compound", by which he meant that it was possible that the wound communicated with the fracture.

3. The consultant took the boy's mother aside and told her that the break was nothing to worry about but that the boy would have to stay in hospital for at least three days because the break in the skin would need penicillin treatment. The house-surgeon did not hear that.

4. There was a regrettable conflict between the house-surgeon and the consultant as to the instructions which he gave her about the treatment of the child. The consultant stated that he instructed reduction of the fracture, application of plaster, and admission to hospital for penicillin treatment. The house-surgeon stated that the consultant instructed reduction of the fracture and a dry dressing on the wound, but said nothing about penicillin. When she asked him whether the little wound was over the site of the fracture he appeared indifferent and made no comment.

5. The house-surgeon interpreted the instructions as meaning that the fracture was to be treated as a simple fracture.

6. When the boy was in the theatre for manipulation, half a million units of penicillin were administered by the house-surgeon, and she also gave him anti-tetanus serum. She explained that she did so on her own responsibility because of the danger of infection; and she also said that she gave verbal instructions that the penicillin treatment was to be continued in the ward.

7. A sister asked her whether the two boys could be discharged in the afternoon of July 3. The house-surgeon gave the boy a full examination, and, being satisfied on all points, authorised his discharge, giving instructions that he should return in four weeks for examination.

The boy's condition deteriorated on July 5. He was hurried back to the hospital, where his arm was amputated to the shoulder-joint as gas-gangrene had set in with such severity as t threaten his life. He did, however, recover with the loss of his arm.

The Lord Ordinary gave judgment for the house-surgeon and the hospitals board, stating that if he had found them negligent he would have assessed the damages at £5000.

On the conflict between the evidence of the house-surgeon and the consultant, the Lord Ordinary said: (*a*) that the house-surgeon "gave the impression in the witness box of being upright and honest"; and (*b*) that "the more natural explanation is that there was some misunderstanding, some failure in communication between the consultant and the house-surgeon, so that the wishes of the consultant about the treatment were not clearly conveyed to the house-surgeon".

The father appealed to the Court of Session, and, from their dismissal of his appeal, to the House of Lords, which dismissed his appeal.

The LORD CHANCELLOR, Lord KILMUIR, said that it was argued against the house-surgeon that she had failed in her duty to exercise reasonable care in the treatment of the child, to take normal and reasonable precautions against infection by giving a proper and normal treatment with penicillin, and to continue the course of treatment for a normal and reasonable period sufficient to avoid the occurrence and development of the infection. It was said that she was in charge of the case from the time when she first examined the child; that if the consultant gave her instructions for a simple fracture and she acted on them, they were unsuitable and improper, as she knew or ought to have known; and that if, without instructions from the consultant, she, independently and of her own volition, chose to administer penicillin, she ought to have known and given the proper course of treatment.

There was no doubt that a mistake had been made in letting the boy out of hospital. But the question was whether the house-surgeon was negligent. There was no doubt that there was a duty on her to display the care and skill of a prudent qualified house-surgeon, it being remembered that such a position was held by a comparative beginner. There was also a duty to carry out the instructions of the consultant, who was on this occasion acting as registrar, unless they were manifestly wrong.

On the conflict between the evidence of the house-surgeon and the consultant, his Lordship found it impossible to disbelieve the house-surgeon. On the probabilities he could not believe that a house-surgeon with her reputation would have refrained from giving the boy the course of penicillin treatment, had those been her instructions. The answer to the fact that she did, of her own motion, give some penicillin, was that she felt herself bound to accept the consultant's view and treat this case as a simple fracture, in which case the patient would be discharged after the operation. But because she was unhappy about the wound, she had decided on the anti-tetanus serum and also penicillin as a prophylactic. It would seem unreasonable, and indeed unreal, to hold her guilty of negligence because she was careful. Moreover, in this hospital compound fractures were treated by her seniors; and she had understood that she had been told to treat this as a simple fracture. Primarily her duty was to follow instructions. His Lordship did not question the authorities which stated that, where instructions were manifestly wrong, duty and common sense combined to say that they must not be followed. But in view of the consultant's opinion in regard to the wound conveyed to her in this case, his Lordship could not say that it was one where the house-surgeon should have disregarded what she believed her instructions to be.

On those facts the father had failed to show that the house-surgeon was " in charge " of the case in the sense of being fully answerable for it, or that she had received instructions to give penicillin, or, expressly or impliedly, to keep the boy in hospital, or that the treatment which she said she was instructed to give was manifestly wrong, or that she had arrogated to herself an independent line of treatment and then failed. The appeal should be dismissed.

Lord KEITH OF AVONHOLM and Lord EVERSHED delivered concurring opinions.

Junor *v.* McNicol and others.—*House of Lords* (Lord Kilmuir, *L.C.*, Lord Keith of Avonholm, and Lord Evershed, *M.R.*). March 25, 1959. Counsel and solicitors: T. P. McDonald, Q.C., and R. Reid (Martin & Co. for J. Miller Thomson & Co., Edinburgh); W. R. Grieve, Q.C., and James Mackay (Le Brasseur & Oakley for Brown Mair Gemmill and Hislop, Glasgow, and Macpherson & Mackay, Edinburgh); A. Thomson, Q.C., and W. M'Ilwraith (Gamlen, Bowerman & Forward for Guild and Guild, Edinburgh).

M. M. HILL
Barrister-at-Law.

Parliament

QUESTION TIME

Hospital Sterilisation Services

Dr. DONALD JOHNSON asked the Minister of Health if he had taken note of the conclusions of the Working Party on Pressure-Steam Sterilisers in its report to the Medical Research Council; and what steps he proposed to take with a view to determining who had the final responsibility for efficient sterilisation of instruments and dressings in a National Health Service hospital.—Mr. DEREK WALKER-SMITH replied: I shall shortly be sending a memorandum to hospital authorities on this matter, including the advice that one member of the medical staff should be charged with the supervision of sterilisation services in each hospital.

Pay of Nurses and Midwives

Mr. GRESHAM COOKE asked the Minister if he would make a statement on new proposals for the pay of nurses and midwives. —Mr. WALKER-SMITH: Revised salaries for all the main grades in general, mental, and maternity hospitals were agreed by the Whitley Council last week and should greatly improve the attraction of nursing and midwifery as a career. The agreement provides increases ranging from £12 to £29 for student nurses, £54 to £87 for staff nurses and midwives, and £105 to £163 for ward sisters and midwifery sisters. Matrons of non-training hospitals will receive increases ranging from £101 to £195, and matrons of nurse-training schools increases ranging from £129 to £237. The Secretary of State for Scotland and I have approved the proposals with effect from March 1. The Whitley Council are now considering the grades not covered by this agreement.

Mr. W. W. HAMILTON: Will the Minister say why it is that whenever nurses have increases in pay, they almost automatically have to pay an increase in lodging expenses, which causes great irritation to them? Will this increase do anything to allay the anxiety of the Royal College of Nursing, which pointed out some time ago that nurses were emigrating to Australia, America and Canada in increasing numbers because of the great disparity in their pay?—Mr. WALKER-SMITH: These charges are, generally speaking, below the economic charge and therefore it is only reasonable that as the pay goes up so should the charges in respect of board and lodging. I would remind the House that these have been agreed by the Whitley Council. Dr. EDITH SUMMERSKILL: Will the Minister keep in mind that every time these excellent nurses and midwives are given an increase it is vitiated by this increase in the charge for accommodation?—Mr. WALKER-SMITH: It is far from true that these increases are vitiated. On the contrary, they represent a very substantial advantage right across the board.

In England Now

A Running Commentary by Peripatetic Correspondents

Ovid once remarked upon the happiness of the man who has broken the chains that hurt the mind and has given up worrying for ever. Moses, the bloodhound, was another blest with the same philosophy. He had the conventional worried look of his breed, somewhat aggravated by being the seventh pup of a functionally six-teated bitch. The rest of the litter adopted the asocial principle of first come first served. He would have preferred a rota system to shield him from anxiety. And then that awful journey in rumbling guardsvans from the warmth of the South Downs, all across London, up to the rugged hills of Lakeland, to be dumped with the milk kits and the papers out on the platform at five in the morning. And then to be called Moses, of all names. Enough to make any self-respecting bloodhound bury his flews in the bulrushes. But that came all okay, for his new owners were Canadians, and soon our village resounded to the musical vowel undulations of Mo.

He grew into a huge slab-sided golden idol, worshipped by the exiles in their tiny cottage by the lake. But he never really lost that worried look. Blocking the full width of the fireplace, he often felt qualms for his owners' missing their homeland central heating. When he was shut out in the garden he slobbered on the windows fretting to come in. When he was in he clawed to get out. He swallowed his master's wrist-watch to pass the time away. He chased the wild deer when he broke the chain. He had to endure the humiliation of paying homage to a usurper in his home when a baby was born. That shook his morale.

Now bloodhounds and babies need a lot of feeding, and the call of the West seemed more satisfying. After all, it was home for most of the family, but to Mo it was an anxious unknown. He brooded over the packing, he fought shy of the gangplank of the ship. He took a dim view of the North Atlantic, and an even dimmer one of the complete absence of trees. No yellow-painted mast, no lovely white stanchion, could trigger off the physiological reflex. Anyway he was not prepared to risk the instability of three legs on a heaving ship. No wonder he retained more than that worried look until the Maritime Provinces hove in sight. Columbus probably celebrated his discovery of the New World in a similar way.

But the trouble did not end there. Although the countryside of Nova Scotia was fine and dandy, the local dogs did not bark the way Mo did. Perhaps he could not pick up the lingo. A lifetime's mental trauma rebounded on his constitution: he ailed, he sickened, and off he went to the happy hunting-grounds of his ancestors. The postmortem showed two duodenal ulcers. So it just goes to show that dogs are not any more human than humans, and maybe Ovid was on the right scent after all.

* * *

Well, according to all the signs, Spring is here. The telescope and weighing-machines are out on the front, and presumably people will soon be thinking of buying some of those summer dresses which have been so temptingly displayed in our local shops since Christmas. The road is up by the swimming-bath and at the present rate of progress there should be a good-sized hole there ready to greet our Easter visitors. The new paint on the railings along by the beach has reached the sticky stage and the half-dozen shelters facing the sea are all set for their annual lick of green paint.

Our U.D.C., obliging as ever, has it all planned. If the Clerk of the Weather will not permit our visitors to get brown the chances are that some at least will get green. But, brown faces or green buttocks, it will be something to take back to remind them of a holiday, and, come to think of it, that is what lots of people want.

* * *

As my peripatetic colleague last week admits, he is still something of a novice with the *retained hot-water bottle*, for his operations have been restricted to the cadaver—the unoccupied bed. Does he know anything of the art of surreptitious removal of the hot-water bottle in vivo—from the occupied bed? In large families it may be taken as an axiom that there are never enough hot-water bottles to go round. As winter advances the discrepancy becomes greater (mortality among rubber bottles being what it is) and I have known one bottle make as many as three changes of bed in the course of the evening until it finally comes to rest on the female side of the parental couch. (Accompanied by a stringless tennis racket turned on edge to allow the heat to circulate. Had you ever thought of that?)

The three methods of extraction in the living or occupied bed are the same as in the cadaver or empty bed. Preliminary localisation by inspection, palpation, and percussion is helpful, but beware and remember the differential diagnosis of small rubber animals which squeak on pressure. The whole operation has to be carried out in complete darkness and in silence, and as the victims may take counter action by lying on or holding the bottle, it requires a combination of the skills of the old-time obstetrician and the practised pickpocket.

* * *

The medical student of today, when he looks round, may well feel that his chance of making a name for himself is small. In the old days it was easy: one kept one's eyes open, dug out a few chronic sufferers from an asylum or some such place, wrote up two or three cases, and sat back waiting for one's name to be affixed. Now, however, one has to invent some such jawcracker as polyesterodiaphysial intussuscipilatory congenesis, and be one of a team of half a dozen people.

Those unselfish characters who still think nomenclature worth while might try using one of those robot machines which they have in America for naming new drugs. It produces short and snappy words at a rate of three thousand an hour. After they have been censored, you may run your eye down the list till you find one that takes your fancy. For instance, the example I suggested above might be called "prodincis" for short.

I have, however, discovered an even better method, and that is my typist. I see from a letter that she put before me today that a young patient of mine is suffering from "fibrolic stenosis". This wonderful name is too good to be wasted. I am now searching for a disease to go with it. Will any toiler who has found or invented a malady and is stuck for a name kindly get in touch with me, and we could make something of it? The typist by the way is good for several more. It was she who reported that one of my patients (a child with pink disease) had phonophobia. My comment on this was that if he was not cured he would surely become a general practitioner when he grew up.

* * *

Keeping the children out of the way while mother sees her patients has long been a problem in our house. The other day I overheard this conversation, between my daughter and a patient.

"How old are you?"
"I'm three."
"And what are you going to do when you grow up?"
"I'm going to be a patient and come and see Mummy every day."

* * *

In the Garden–v

TROUBLE AMONG THE ROSES
or
HATS OFF TO *Otiorrynchus singularis*

Though my face may be clay-coloured and though puce is my pubescence
Though not as big, with bright red legs, as Cousin *clavipes*,
Yet when all is said and done the main point is—the essence—
I'm the lesser of two weevils, look at it how you please.

Letters to the Editor

FAILURE OF STERILITY IN HOSPITAL WARD PRACTICE

SIR,—The paper by Dr. Darmady and his colleagues (March 21) is yet another indictment of hospital sterilisation procedures and is perhaps the most damning in the series in that it roundly accuses one hospital of using instruments and dressings only half of which are sterile. Since it is obvious that the failure of a process that should be infallible was due for the most part to faults in operation or maintenance, hospital management committees may take alarm at so much human frailty amongst their staffs and be stampeded into installing central supply rooms to take sterilisation out of the wards altogether.

I hope that none of them will be deluded into thinking that thereby they are doing something that will reduce the high incidence of infection acquired in hospital. Present indications are that most of these infections are due to organisms on the fingers or clothing of nurses or doctors that have come from themselves or someone else and not to organisms surviving on inadequately sterilised instruments or dressings. Indeed, quite low temperatures for very short periods of time will suffice to kill the organisms responsible for these infections.

Staphylococcus aureus, for example, is killed in less than five minutes in water at only 60° C. *Streptococcus pyogenes*, *Escherichia coli*, and *Pseudomonas pyocyanea* cannot be very much more resistant. And in this connection it is noteworthy that although Dr. Darmady and his colleagues found that 241 articles were contaminated in the hospitals they studied, *Staph. pyogenes* (*aureus*) was isolated from only 5 and coliforms from 2, while *Strep. pyogenes*, *Proteus vulgaris*, and *Ps. pyocyanea* were conspicuous by their absence. Since we can assume that many of the articles they sampled had been contaminated by so common an organism as *Staph. aureus*, if not by the others mentioned above, before they were submitted to the sterilisation procedures employed in the seven hospitals, it follows that these procedures, inadequate as they appeared to be, were evidently quite sufficient to rid almost all of these articles of the organisms that cause sepsis in wounds.

One can, therefore, only conclude that the installation of central supply rooms with autoclaves substituted for boiling-water baths in the wards is not likely to do very much more than provide better protection against the spores of organisms such as *Clostridium tetani* or *Cl. welchii*. Whether this extra protection is worth the expenditure of money and effort is a matter for serious consideration because cases of tetanus and gas-gangrene clearly due to spores still surviving on instruments, &c., after full immersion in boiling water for three or more minutes must be extremely rare.

Except for the fact that the spores of some organisms may survive, there is, bacteriologically, very little wrong with the hospital boiler or "steriliser". But it is all too obvious from the Nuffield report and further emphasised in the paper by Dr. Darmady and his colleagues that not only are many hospital sterilisers badly sited, damaged, and improperly operated, but that the autoclaves and those in charge of them are equally unsatisfactory.

No-one would like this state of affairs to continue, but I know from personal experience that none of the faults found by the investigators are irremediable. For, about ten years ago, I was asked to inspect and report on the sterilising procedures in use at St. Thomas's Hospital. There were many things that were wrong but it took very little effort and very little money to set matters right. My own time amounted to no more than six sessions of about an hour each with the sisters concerned. It took very little

longer to write the report, followed by a meeting of all interested parties, and a few visits of inspection to see that the suggested alterations had been carried out.

Given the same cooperation that I received from all concerned, I see no reason why any hospital bacteriologist could not achieve the same end with no greater expenditure of time and effort. It would certainly be quicker and would cost very much less money than that required for the equipment and maintenance of a central supply room.

There is, actually, much to be said for the retention of the boiling-water steriliser, albeit properly operated, in the wards and outpatient departments because the sterilisation of instruments in such a piece of apparatus should form an important part of the education of nurses and medical students. If they become dependent on prepackaged goods from a central supply room, they will have to learn a whole series of new techniques when they go out into the world to look after patients in places far distant from central supply rooms. Since they will inevitably do them badly unless they have had constant practice while training, we may be faced with a whole series of new problems in the future which we have created while solving—or thinking we are solving—one.

Department of Bacteriology,
St. Thomas's Hospital Medical School,
London, S.E.1. RONALD HARE.

THE FUTURE OF CHILD GUIDANCE

SIR,—Your editorial of March 21 contained severe criticisms of the latest circulars of the Ministries of Health and Education without, I feel, much appreciation of the problems of providing child guidance and preventing maladjustment and delinquency in the community.

There can never be sufficient psychiatrists, psychologists, and psychiatric social workers to meet the needs of the country, so that the service must be ready to help those who work closely with children and their families —teachers, health visitors, social workers, and the parents of children without problems, as well as the parents and children whose difficulties will bring them to the clinic. If this is to be attempted the neighbourhood served by the clinic must be limited, and indeed the need to provide for attendances weekly, or more frequently, over a long period by families who, in the nature of things, are likely to be often uncooperative, demands a similar limitation, and this area containing, it is suggested, about 15,000 schoolchildren is much smaller than the gathering-ground of any children's hospital, so that clinics based on something more than children's hospitals are required.

We have all suffered so much from fragmentation that any attempt to marry the sections of the health services of this country deserves support, and I should have thought that local-authority clinics directed by psychiatrists working for teaching hospitals or regional hospital boards had proved so successful as to be a pattern for other forms of cooperation, nor should I have thought the provision in Ulster a model for us. As you say, the service badly needs more staff; but the ring of child-guidance clinics in hospitals in the centre of London, unassociated with any particular area and unable to do more than deal with the children referred to them often from long distances, is not a happy example of the effective use of staff.

It may be that the objections to the use of hospitals for these children have been overemphasised, but the problems of child guidance are problems of child rearing and in the end have to be solved in the home. The suggestions of the Underwood Committee and these circulars could help to do this.

Plumpton, Lewes, Sussex. DENIS PIRRIE.

SIR,—The problem of the child-guidance services is more complex than you allow in your leading article. Most child psychiatrists, it is true, suffer from " isolation in space and in thought from their colleagues both in psychiatry and in pædiatrics ". On the other hand, child guidance is different from and more than child psychiatry. It is not purely a medical specialty, but in it are fused psychiatry, psychology, and sociology. It is a service for the welfare of children in its widest possible aspect, and it is doubtful whether the main work of a well-established clinic is " to examine and treat *sick* children ". After some years one finds that prophylaxis is gaining on therapy.

Child guidance needs a number of people and a great deal of space. Hospitals find it hard to supply these needs. A headmaster told me of his surprise, the other day, to find a great child psychiatrist in a great children's hospital " poked away in a dark little cell ". In that particular hospital there are a number of cells for the psychiatrist and her assistants. In my own hospital the only space that can be made available for psychiatry—for adults and children—is a hut with four extremely small rooms. By way of contrast, in the clinic in which I am " supplied " by the regional hospital board, the local education authority has provided a house containing fourteen rooms, two " sub-clinics ", each with two rooms and waiting space, and each of the three has a large garden. This clinic serves the community in the area, has close links with general practitioners, teachers, probation officers, the children's department and other social workers of both statutory and voluntary organisations, and has, as well, the closest cooperation with the local education and health authorities.

I myself would not put either local child-guidance work or hospital work before the other. Both are important, indeed essential, but they are different. To equate child guidance and child psychiatry is to perpetuate a confusion which can only lead to misunderstandings and dissatisfaction.

London, W.C.1. PORTIA HOLMAN.

SIR,—I was glad to read your very fair and constructive leader. I trust you will not think me ungrateful if I pass by the main recommendations, with which I largely concur, and focus on the problem of whether or not the child-guidance clinic should be made directly accessible to parents.

This question of " free referral " is one, I consider, where psychiatrists and pædiatricians have sometimes let imagination run away with itself. Dark forebodings have been voiced on the evils of this principle—how it would release a torrent of new cases onto the already swollen clinic waiting-list, how these cases would be untreatable (and therefore a waste of time to see), and how this would represent yet another scheme to whittle away authority from the family doctor.

My own experience suggests that these fears are exaggerated. Certainly, in my present child-guidance clinic (York City) free referral has been available to parents since its inception in 1941 without the occurrence of these anticipated difficultes. In fact, the actual proportion of such parent-referred children has never been large; in 1958, a fairly typical year, their total was 11% of all clinic referrals. Nor does the clinic team find such

children " bad cases ", nor the parents later more prone to become uncooperative. Finally, I would very much doubt if this policy has poisoned our relationship with family doctors. Certainly, those I have spoken with have without exception been most helpful and friendly.

I would entirely agree with the concept of the family doctor as one of the main " filters " for the child-guidance clinic, treating children with the simpler emotional disorders and referring their more difficult problems. The principle of free referral does not replace this, but rather acts as a safety-valve, so that the distraught parent who arrives at the right place without the customary formal introduction need not be turned away.

Child Guidance Clinic, York. C. H. NEVILLE-SMITH.

THE RIGHT KIND OF CONTROL

SIR,—Your annotation of March 21 sounds a timely warning against too great reliance on the " controlled trial " as currently conducted in the attempt to assess new remedies.

Introduced into clinical medicine during the late 'thirties, statistical method did much to counteract the naïve enthusiasm for new therapy which often reached the dimensions of a " craze " sweeping through the whole profession. Unfortunately, statistics has now become almost a craze in itself and uncritical acceptance of a statistician's verdict is stifling initiative in many fields of work. Originally introduced into clinical research as an aid to rational thought, statistics is nowadays regarded almost as a substitute for rational thought.

London, S.E.13. ALLAN CHATELIER.

FLUORIDATION IN NEW ZEALAND

SIR,—There seems to be some misconception about the ability to add fluorides in controlled amounts to water-supplies. As you say in your annotation of March 14, " fluorides present their own special problems ", but it is also stated in the report of the United Kingdom Mission to North America that the " controlled addition of fluoride presents few difficulties that have not already been met and overcome ".

This can be illustrated by the results obtained at the fluoridation study areas in this country. The fluoridators installed utilised the experience gained in the United States, and modifications and indeed new procedures were developed in this country and put into practice.

The table below summarises the results obtained, and includes both the addition of sodium fluorosilicate by a volumetric solid feeder and that of sodium fluoride by a saturator and a chemical proportioning pump. The aim was to produce a mean slightly below 1·0 p.p.m.

	Watford		*Kilmarnock*		*Anglesey*
	Solid feeder	*Saturator*	*Solid feeder*	*Saturator*	*Saturator*
No. of samples examined		Over 1500		Over 1300	Over 1400
Mean value (p.p.m. fluoride as F)	0·90	0·93	0·96	0·95	0·91

No results greater than 1·1 p.p.m. were found, and at all three places over 90% of the results were at the desired level, allowing for the experimental errors of the method used to determine the fluoride. These figures were also in close agreement with those calculated from the amounts of fluoride used and the volumes of water pumped.

It would indeed be unfortunate if, as the result of an article in *The Lancet*, a doubt was raised in anyone's mind as to water-engineering aspects of fluoridation.

Department of the Government Chemist, London, W.C.2. J. LONGWELL.

THE CRANBROOK REPORT

SIR,—Your leading article of Feb. 21 on the Cranbrook Report gives admirably fair and balanced comment: the views expressed by Mr. Wrigley and Mr. Garland (Feb. 28) with such clarity have been welcomed by many who have remained silent; indeed, the " audible silence " in which the report has been received is surprising—is it due to satisfaction or to despair?

Mr. Frank Cook (March 7) is critical of the ventilation of views on the report in *The Lancet*. While we must all share his impatience with " the endless altercations as to who shall deliver the baby and where the baby is to be delivered ", yet this is an inescapable issue in the evolution of the best maternity service, and it is necessary to " take sides "—i.e., to come to a decision. Any decisions arrived at must command as wide a field of consent as possible, because good will depends on it, and an efficient service depends on good will.

No-one reading the Cranbrook Report can fail to be impressed by the difficulties the committee has had to face in the shape of conflicting opinions at every stage. In addition, the subtle devil of complacency lurks in the basically good results obtained statistically by the present service. In spite of this, the avoidable infant and even maternal deaths which still occur act as a spur of an entirely different order to that produced by the position of a decimal point in a numerical column. Furthermore, the stationary stillbirth-rate remains a standing reproach.

I share the disappointment of Mr. Wrigley and Mr. Garland in that, while the report states " in the light of experience gained during the 10 years since 1948, it is probable that the majority of us would suggest that a unified service . . . might be a desirable arrangement " (which is in agreement with the views of the Guillebaud Committee), yet their recommendations are clean contrary to this ideal, and recommend the retention of the tripartite service!

A final point should be made: the committee has been in difficulties from a plethora of opinions and a dearth of facts. Is it not desirable to consider what facts are required for objective consideration, and to recommend what measures should be employed to obtain these as quickly as possible? In a matter where none of us are devoid of prejudice, this seems to be essential.

General Hospital, Ashton-under-Lyne. T. B. FITZGERALD.

" AUTO-IMMUNITY "

SIR,—I read with interest your leading article of Feb. 21. Your comment that the inclusion of Freund's adjuvants with rabbit thyroid extracts might influence the production of antibodies against the rabbit's own thyroid is worth consideration.

In January of this year I reported [1] the results of an attempt to produce experimental thyroiditis in 18 rabbits immunised with rabbit thyroid extracts and Freund's adjuvants. The injection programme was that used by Witebsky,[2] with one exception. The commercial ' Difco ' [3] Freund's adjuvant was used containing a quarter the concentration of *Mycobacterium butyricum*. Hæmagglutination titres were estimated at three-weekly intervals for seven months.

Only 8 rabbits produced antibody against thyroid extract. 4 of these, after reaching a maximum titre at approximately four months, demonstrated a progressive fall over the next three months. These are still being followed. Four other

1. Proceedings, Western Regional Group, Division of Medical Research, National Research Council, Canada. Banff, January, 1959.
2. Witebsky, E., Rose, N. R. *J. Immunol.* 1956, **76**, 408.
3. Difco Laboratories Inc., Detroit, Michigan, U.S.A.

animals were sacrificed three to four months after immunisation, when antibody titres in excess of 1/2000 were demonstrated. In the thyroid of 1 animal, focal accumulation of lymphocytes were seen. The remaining 3 showed normal histological appearances. Intravenous injection of thyroid extract without Freund's adjuvant in other series of rabbits has not resulted in antibody formation.

This work has been extended using Freund's adjuvant containing a higher concentration of tubercle bacilli, but results are not yet available.

Department of Pathology,
University of British Columbia,
Vancouver.

W. E. SHEPHERD.

BONE-MARROW GRAFTS IN HUMAN DISEASE

SIR,—May I correct one misstatement in your otherwise excellent leader of Feb. 28? You state: "Thomas et al. think that the 400–600r range is dangerous and give reasons for limiting the dose to 200–300r." We did say that the 400–600r range is dangerous: we believe, however, that it is necessary to go to higher levels of irradiation, not lower. We stated: "In most instances the patient may be expected to require nice adjustment of ionizing effects in the 800–1000r range to secure beneficial clinical effects."

Mary Imogene Bassett Hospital,
Cooperstown, New York.

E. DONNALL THOMAS.

PRISON MEDICAL OFFICERS

SIR,—As you are probably aware, there has been a recent realisation among prison medical officers that all is not well in their chosen field of endeavour. This appreciation is gradually coming to the notice of the wider public through both the national and medical Press.[1 2] I should be pleased, therefore, if you would allow me to state briefly one considerable cause for anxiety amongst those of us working for H.M. Prison Commissioners, as well as uttering a warning to any medical man pondering the Prison Service as a career. This cause of anxiety can, for want of a better phrase, be termed "professional status".

At the present time a doctor is recruited into the Prison Service as a medical officer regardless of his qualifications and experience. He may, but may not, be usefully employed as regards his particular expertise. Whatever else happens he will certainly tend to become a "jack of all trades and master of none". He will possibly double the role of specialist psychiatrist who gives expert evidence with the general treatment of illness and, as a sideline, be expected to approve or condemn food, as well as other public-health duties. This state of affairs cannot be accepted as either desirable or efficacious, and from almost any point of view it would seem reasonable that a certain number of doctors *within the Service* should be specialist psychiatrists. However undesirable the present position may be, anxiety is provoked by the general impression that more and more of the specialist psychiatric work related to H.M. Prisons will be taken over by specialists from outside the Prison Medical Service on a sessional, or even, maybe, a full-time basis.[3]

Who will staff the observation and remand centres? Who will run and staff the East-Hubert Institute? Who will plan and carry out research? It is generally felt by the prison medical officers that it will not be they but rather psychiatrists imported from the National Health Service who will play the larger part in the modern assault on delinquency and criminality. Is this fair? I would submit that it is not. There are medical officers in the service who are qualified as psychiatrists, and many more who could be in a very short time—if given the chance. Why are these persons not being given an opportunity of becoming really competent at their job so that in the future they could run an efficient Prison Psychiatric Service? Why is nearly all the research in prisons being carried out by groups outside the service without any real or official *participation* by the prison medical officers, thus denying them experience in this field?

I suggest that in a very short while the prison medical officer will be nothing more than a G.P. cum psychiatric registrar for the remainder of his life. Further, that this appalling state of affairs rests fairly and squarely at the feet of the Prison Commissioners and the little group of medical personnel in Horseferry House. It is these persons that, in the words of Emile Zola, "J'accuse".

WHITE SLAVE.

1. *Daily Telegraph*, Feb. 19, 1959.
2. *Brit. med. J.* 1959, i, suppl. p. 86.
3. Snell, H. K. Quoted in *Lancet*, 1958, ii, 1116.

CIRCULATION OF THE BLOOD

SIR,—I am interested in Dr. Grant's suggestion in your issue of Feb. 14 that the circulation may be assisted by active contraction of the arterial tree, producing a "milking effect".

Heyman [1] reported the presence of distinct arterial "undulations" in the upper limbs of patients with atrioventricular heart-block. These undulations bore a constant relation to the P-waves in the E.C.G., and were thus independent of the main pulse wave. They disappeared on treatment with tetramethylammonium bromide, suggesting their nervous origin. Heyman concluded that these undulations were probably actively propagated down the artery at the same velocity as the pulse.

In the embryo, before the heart develops, the circulation presumably functions by the rhythmic contraction of the blood-vessels. The heart may be considered as a specialised "blood-vessel", with specialisation of these functions of rhythmic contraction and relaxation. But this does not necessarily imply that the blood-vessels have lost their primitive functions.

Rhythmic peristaltic contractions of arteries [2] and veins [3] have been described in the past, but their possible importance as factors in maintaining the normal circulation have not, to my knowledge, yet been critically determined.

Department of Physiology,
Faculty of Medicine,
University of Natal,
Durban.

MICHAEL HATHORN.

THE GASTRO-AURICULAR PHENOMENON

SIR,—Concerning the article by Malherbe [4] on hiatus hernia associated with itching in the auricular external meatus, Dr. Engel (Feb. 14) has discussed the gastro-auricular phenomenon described by him in 1922. His syndrome consists of distressing itching in the ear in persons suffering from heartburn due to hyperacidity. The itching is immediately relieved by taking bicarbonate by mouth.

I should like to mention a similar syndrome also associated with hyperacidity. During the past few years I have observed some 10 patients, including myself, who have shown the combination of heartburn and an imperative coughing attack following an intense feeling of pricking in the upper part of the trachea and in the larynx. I suppose that the same mechanism might operate as Dr. Engel suggests in his cases—namely, that an "intraneural short-circuit" (or, perhaps better, "intraneural induction") takes place between different afferent fibres in the vagus nerve, which results in a projection of a

1. Heyman, F. *Acta med. scand.* 1955, **152**, 91.
2. Cornwall, E. E. *Med. Times, N.Y., Long Is. med. J.* 1933, **61**, 268.
3. Burch, G. E., Murtadha, M. *Amer. Heart J.* 1956, **51**, 807.
4. Malherbe, W. D. F. *Lancet*, 1958, i, 1368.

tingling sensation in the laryngeal and tracheal mucosa respectively in the external meatus of the ear.

Direct stimulation of these respiratory areas is probably excluded by the fact that in no case was there regurgitation of acid stomach contents into the hypopharynx; the heartburn was confined to the level of the cardia. As in Dr. Engel's cases bicarbonate alleviated the cough at once in this " vagovagal " syndrome.

Central County Hospital,
Falköping, Sweden. RAGNAR BERLIN.

CHILDREN IN HOSPITAL

SIR,—Dr. Lawson (Feb. 21) appears to cast a sinister light on the activities of the Committee on the Welfare of Children in Hospital which I, for one, am unable to detect in the report. The committee had to reconcile various facts which appear to me to be reasonably clearly stated in paragraphs 28–34.

There are children in adult wards—which seems to be a bad thing.

The evidence presented to the committee laid a great deal of stress on visiting. This seemed to be a good thing.

Centralisation of children's beds in big teaching children's hospitals is perfectly possible in an area of large population with good transport facilities. Quite a lot of children, however, do not live on a direct bus or train route to a big children's hospital. The need for visiting being agreed, they are admitted to the nearest place where they can get inpatient treatment and be visited. At the moment this often means an adult ward which also accommodates the senile and the dying, so that the child may witness and overhear things which we would not wish for our own children. It seemed more practical to suggest that the hospital with ten children scattered in five wards should collect them into one ward, than that they should put them into an ambulance and send them to a centre farther away from their parents. Management committees would seem more likely to do this than to create new children's hospitals.

It would be interesting to know whether the debates in the House of Lords and the correspondence in the Press have filled the empty beds in the children's hospitals. One suspects that they have not, and that Dr. X and Dr. Y are still admitting children in the area blindly to their adult beds so that the parents can visit. It is not the Machination of a Wicked Committee that has created the hiatus: it looks more like a lack of communication between the pædiatricians and the others, and a more understanding attitude to parents and children on the part of doctors generally.

Paragraph 16 of the report points out that " a special study of children in mental and mental deficiency hospitals was not made " . . . but that the recommendations in the report applied to them. This paragraph might be read as ending the policy of apartheid which has relegated the child defined as defective to a C stream in medicine. Certain of the lay Press comments on the proposal that patients from the Fountain Hospital be moved to Queen Mary's preserved the apartheid barrier, and implied that this move downgraded Queen Mary's. Dr. Lawson obviously believes this. A comment in the *New Statesman* did not point out that the Fountain patients are children and implied that the expert nursing and teaching services would be wasted on " mental patients ". Surely mental deficiency is a branch of pædiatrics. Recent work has shown that many of these children may be suffering from defects in communication rather than in general intellect, and that the metabolic factors in deficiency are at least interesting. Is it not time that we housed these children in the good empty children's wards set in green fields, and that we used all the resources of modern pædiatrics to solve the clinical problems they present? When I was a student at Queen Mary's the spastic child was only just emerging from the mental-deficiency ragbag. The others will not come out unless they are given the same intensive study as the spastic children.

London, W.2. ELIZABETH TYLDEN.

SIR,—Statements about Queen Mary's Hospital for Children, Carshalton, are being made by people who have not been there for a long time. May I correct two errors?

Sir Harry Platt (Feb. 28) remembers the long-stay hospital he visited 40 years ago and considers the present scarcity of cases of the type then treated relevant to the present discussion. But it was a realisation of this scarcity that led to the development of the hospital as a general hospital for children several years ago. It now copes with modern requirements in hospital pædiatrics from emergency surgery in the newborn to chronic medical conditions in adolescence.

Lord Cohen (March 14) suggests that the acute cases could be dealt with as well in general hospitals with " adequately equipped children's units ". This point has been discussed elsewhere, but it is not the point at issue. The proposal was to transfer the patients to existing accommodation in the area—by no means all of which would fit this definition—and apparently as a matter of short-term financial expediency.

London, W.1. H. H. NIXON.

PANIC AND PHOBIA

SIR,—Dr. Goodall (March 21) is right. On the description the patient *could* have had malaria. But I don't think he had. After half an hour's talk and the psychological " exercises ", his symptoms had quite left him, and he was able to escort me downstairs. Malaria, I fancy, is more difficult to treat.

Student Health Association,
University College London,
London, W.C.1. NICOLAS MALLESON.

PATHOGENESIS OF CANCER

SIR,—To those of us who believe that the real problem of the pathogenesis of tissue malformation lies as much in the general metabolic and hormonal change as in the local transformation, the views of so experienced a worker as Professor Smithers, given in your issue of March 21, are particularly gratifying. I should, however, like to comment on one or two points.

Firstly, it was Schinzinger who first, in 1887, removed the ovaries in a case of carcinoma of the breast—he thus holds precedence over Beatson by 7 years. Secondly, some modification must be made in Loeb's original cancer formula $H \times S = C$ (H meaning heredity constitution, S standing for stimulation, and C for carcinoma). I have suggested that T.H. (thyroidal constitution) be substituted for the H in the formula, for there now seems little doubt of the importance of this gland in the growth of tumours—its secretion appears to be actively protective in this respect. Hyperthyroid subjects are much less liable to carcinoma than hypothyroid and post-thyroidectomy patients, and the longer the gland continues to counteract the ageing processes in its own vessels coincident with middle age, the later will any tumour appear.

The role of other hormones is of equal importance in this connection, for, like thyroid, their deficiency appears to alter the cell metabolism of the particular tissue affected so as to

permit malignant change. Contrariwise, as I have shown with Warburg's method, the addition of such hormones to already malignant cells does seem to modify their metabolic activity profoundly.

I think I was the first to apply this idea in clinical practice, by using the sex hormones to influence local cell growth, the idea being to stimulate oxidation and so rob the malignant cell of its basic energy fermentation. The results obtained at that time have been amply confirmed by other workers, and serve to emphasise the all-important role played by the hormones as the modulators, if not the actual regulators, of all cell enzyme and metabolic activity.

London, W.1. ALFRED A. LOESER.

CONSUMER INTERESTS

SIR,—I should like to express my full agreement with the very cogent remarks by Professor Black in his article of March 28.

Our partnership of four practitioners is one of those selected for the introduction of students into general practice and I find the 14 days twice a year allotted to final-year students ideal for this purpose.

Whatever the eventual destination of the recently qualified doctor—and the statistical 25% entry only into general practice surprised me—I think that this introduction to the G.P.'s work is most beneficial to student and incidentally to general practitioner. The method chosen and the care in selection in Manchester of the right student for the right practice has everything to commend it.

I am certainly looking forward to it becoming a permanent institution in medical education.

Manchester. P. T. WEYL.

PSYCHIATRIC SEMINARS FOR GENERAL PRACTITIONERS

SIR,—I should like to associate myself with the sentiments expressed by Dr. Lask in his letter of March 21.

I was house-physician in the psychiatric department of my teaching hospital, I underwent a year's training from excellent psychiatrists before being graded as an Army psychiatrist, and I have thirty years' experience of general practice. None of these disciplines has been of as much value to me in understanding and treating the emotional aspects of my patients' illnesses as a course of seminars at the Tavistock Clinic.

I would emphasise that the seminars do not make family doctors into psychiatrists, but help them to deal with the emotional elements that are present in all illness.

It is practically impossible for the student to get this type of experience at present in his undergraduate training. Everyone agrees that the function of the family doctor is to understand and treat the whole man. It appears that doctors who feel the need for further education in psychotherapy must go it alone.

One would have expected the British Postgraduate Medical Federation to give this pioneering effort at a growing-point of medicine their enthusiastic support, and it would be interesting to know why it is denied.

London, E.11. SIDNEY ABRAHAMS.

SIR,—I should like to support Dr. Lask's letter of March 21.

I was the fortunate recipient of a fellowship which allowed me to attend fourteen of the seminars for general practitioners at the Tavistock Clinic during February, and while a short concentrated course is not ideal, it was very much better than nothing, which was the only alternative to me for geographical reasons. Fuller information about these seminars is contained in Dr. Balint's very interesting book *The Doctor, The Patient and His Illness* which I think should be read by every G.P.

The advantages to the nation in the reduction of the drug bill, to the patient in better treatment, and to the doctor in greater satisfaction in his work, makes encouragement of these seminars so important that official recognition is in my opinion inevitable, further delay being pointless. Similar seminars should be started in other teaching centres and G.P.s given every encouragement to attend.

Brora, Sutherland. E. J. R. PRIMROSE.

MENTAL HEALTH BILL

SIR,—Under this Bill it seems possible that there may be an opportunity of reorganising the administrative arrangements in mental hospitals to allow individual consultant psychiatrists full responsibility for their patients, on a basis similar to that already established in general hospitals. This will mean a modification of the present mental hospital medical-superintendent system, although it does not necessarily follow that superintendents will lose in status in any revised arrangement.

There are clearly many factors of major clinical significance involved in such a change, and they probably apply to psychiatric work in general hospitals as well as in the mental hospitals. We feel that consultant psychiatrists who are not medical superintendents may welcome opportunities of discussing these factors, and perhaps formulating views which may be put forward more effectively if they represent the results of considered group discussion rather than the views of single individuals.

We should therefore like to invite senior clinical colleagues in this category who are interested in taking these questions further to send their names to one of the undersigned. Depending on the results of this invitation we should undertake to try to arrange for occasional discussions on a tentative basis, and if it seemed helpful to report any conclusions reached.

Taunton.	M. F. BETHELL
Hornchurch.	R. W. CROCKET
Oxford.	JOHN E. DUFFIELD
London.	A. HARRIS
Ipswich.	J. G. HOWELLS
Coulsdon.	JOHN T. HUTCHINSON
Warwick.	C. TETLOW
Sutton.	A. S. THORLEY.

SIR,—A few of the letters on this topic seem to confuse two issues which should be treated separately. The first of these is the relationship of the medical superintendent to patients who are compulsorily detained in hospital but are not under his clinical care, but that of another consultant. The second is the question of hospital administration. The Bill "... repeals the principal existing Acts ..." and "... specifies the circumstances in which mentally disordered persons may be compulsorily detained in hospital ..." It does not concern itself with the question of administration of hospitals, and therefore the second issue mentioned above does not fall within the Bill's reference.

As regards the first issue the Bill states that all responsibility for the patients, clinical as well as legal, will rest with the medical officer in whose care the patient is. That means the consultant psychiatrist. I was interested to read Dr. Munro's statement (March 14) that his Association has taken care to emphasise the definition of the "responsible medical officer" in that sense. In the report to the Royal Commission they pleaded for the retention of the legal responsibility in the hands of the medical superintendent. I believe that all of us who welcome this Bill owe his Association a great deal for their imaginative proposals contained in their report to the Royal Commission. I am glad to see that on this one

point which caused some regret they have now changed their policy.

The old proposal of the Royal Commission to make the "responsible medical officer" the medical superintendent would really be unworkable. Under the new Bill patients who are liable to be detained will often be admitted to general hospitals which have no superintendents. On the other hand, there are a few general hospitals which have superintendents who are doctors but not psychiatrists. It would be absurd to make them legally responsible for renewal of, or discharge from, detention (which appear to be the new terms for recertification or decertification). The only doctor who can meaningfully assume that responsibility is the consultant psychiatrist who is in charge of the patient's treatment. If a special rule in respect of special legal powers of the superintendent were to be applied to the mental hospitals—and there is nothing in favour of it—these hospitals would have to be once again "designated". The de-designation proposed in the Bill, which is one of its great advances, would thereby be lost.

As regards the question of administration of mental hospitals, this is unaffected by the Bill. It seems to me that there are both advantages and disadvantages in the various proposals made by your correspondents. Perhaps the question should be left to each hospital to solve in their own way. The decision would rest with the medical advisory committee, the management committee, and the regional hospital board, who come to an agreement between them. There seems to be a growing group of consultants *and* superintendents who feel that the medical superintendents in mental hospitals should be replaced by non-medical administrators. It goes against the grain of any consultant physician to have another doctor—some kind of super-consultant—interfere in his relationship with his patient. If, however, the superintendent is not obliged by law to do that any more there may be many consultants who at the present juncture prefer a doctor at the head of the administration to a lay administrator.

University Department of Psychiatry,
The Royal Infirmary, Manchester. J. HOENIG.

MEGALOBLASTIC ANÆMIA IN PREGNANCY

SIR,—Dr. Forshaw's letter of Jan. 10, in which he comments on our experience with megaloblastic anæmia of pregnancy, was of great interest to us. His remarks on the normal blood-group distribution in megaloblastic anæmia of pregnancy and the puerperium stimulated us to compile a similar survey of our own cases.

The blood-group distribution of 100 cases of megaloblastic anæmia of pregnancy is contrasted below with that of 1000 random antenatal patients who were not suffering from the disease.

Blood-group	*Megaloblastic anæmia*	*Controls*
O	42·0%	45·6%
A	51·0%	42·9%
B	5·0%	8·3%
AB	2·0%	3·2%

These figures suggest an increase of group A in our series of megaloblastic pregnancy anæmias, already known to exist in addisonian pernicious anæmia. However, the series is as yet too small to draw any conclusions from it which could be regarded as statistically significant. It might perhaps be of interest to note that 7 out of 9 patients who showed diminished fat absorption belonged to group A.

Only a nationwide survey of megaloblastic anæmias of pregnancy could establish an accurate blood-group distribution on the lines of the investigation of blood-groups in pernicious anæmia by Professor Aird and others.[1]

City General Hospital,
Stoke-on-Trent. C. GILES
EILEEN M. SHUTTLEWORTH.

1. *Brit. med. J.* 1956, ii, 723.

A REMEDY FOR AGEING?

SIR,—I have read with great interest your annotation of March 14 referring to the work of Aslan and Vrbiesco.

I agree that the claims may well be exaggerated, but I have had very encouraging results from an improved form of H3, produced by a German firm and called 'Ruticain'. Ruticain is a compound of procaine, vitamin B_{12}, and rutin (a flavonoid); and I have now treated ten patients with the preparation (their ages ranged from 60 to 75). I have found that the presenile cases especially have responded very well; tiredness, depression, and tremor of the hands disappeared after thirty injections, and memory, which was very much impaired in four cases, has improved considerably. All the patients came to my consulting-room for treatment and continued to lead their normal lives, and I feel confident therefore that the improvements were not due to rest or suggestion.

No definite conclusions can be drawn from ten cases, of course, but the results do support your suggestion that the time has come for properly controlled trials to prove or disprove the value of these new methods of treatment in relation to the problems of senility.

London, W.1. MAX ODENS.

INTRAGASTRIC ADMINISTRATION OF OXYGEN

SIR,—During a study of the absorption of oxygen from the gastrointestinal tract of premature and newborn infants, we made the following observations which may be of interest to your readers:

A 20-week-old fœtus weighing 400 g. was delivered prematurely of a mother with antepartum hæmorrhage. Initially the infant made a few feeble ineffectual gasps, but remained limp and cyanotic. Nevertheless, the heart continued to beat and several minutes later a tube was passed into the trachea and the lungs were gently expanded under positive pressure. Within seconds the skin became pink, tone and movement appeared in the limbs, and regular respirations ensued. Blood drawn from a small catheter inserted through the umbilical artery into the aorta was 93% saturated with oxygen and had a pH of 7·24. The mean aortic pressure, measured with a saline manometer, was 33 cm. Intragastric oxygen was then administered at 1 litre per minute. When gas was returning well from the escape tube, the endotracheal catheter was occluded. Three minutes later the aortic oxygen saturation was 24% and after five minutes had fallen further to 8%, the pH being 7·10. The infant appeared dusky and limp. Upon reopening the endotracheal tube and reoxygenating the lungs the infant dramatically recovered. His oxygen saturation rose to 94% and his pH to 7·25.

In view of the many clinical impressions regarding the efficacy of intragastric oxygen for resuscitation, these findings are somewhat thought-provoking.

Columbia-Presbyterian Medical Center,
New York. L. S. JAMES
F. MOYA
E. D. BURNARD
V. APGAR.

Appointments

CURRIE, A. B. M., M.B. Glasg., F.R.C.S.E.: senior casualty officer, Greenock Royal Infirmary.

KLEE, D. W. S., M.B. Lond.: assistant M.O.H. and school M.O., Dudley.

LEE, J. E., M.R.C.S.: assistant M.O. and school M.O., Batley and Heckmondwike, Yorkshire.

O'LEARY, D. C., M.B. N.U.I.: school M.O., Durham.

TINNE, J. E., M.B., B.SC. Edin., D.P.H.: consultant bacteriologist, Glasgow Royal Infirmary, and honorary lecturer, Glasgow University.

WARD, BRIAN, M.B. Manc., D.P.M.: assistant senior M.O., Leeds Regional Hospital Board.

Obituary

THOMAS MURRAY NEWTON

M.B. Glasg., F.R.F.P.S.

Mr. T. M. Newton, formerly surgeon to the Western Infirmary, Glasgow, died on March 19 at the age of 68.

He was born in Glasgow and graduated M.B. at Glasgow University in 1913. In 1914 he enlisted in the R.A.M.C., serving throughout the war in France and Mesopotamia. On demobilisation he entered general practice in Grimsby, but after several years returned to Glasgow. He became an F.R.F.P.S. in 1925. In 1927 he joined the surgical staff of the Western Infirmary as an extra dispensary surgeon, and in 1945 he gained charge of wards. He was the original chairman of the Central Consultants and Specialists' Committee of Scotland. He retired in 1956.

T. B. G. writes:

"Though Murray Newton's interests were wide and varied, he specialised in surgery of the thyroid gland, a field in which he was held in high repute. He brought to the practice of surgery the shrewd judgment he had developed in his years of general practice—a judgment that was always tempered by his great humanity. Though appreciating the need for specialisation, he was at pains to impress on his younger colleagues the need to treat the patient as a whole. His counsel and guidance were frequently sought by his students and juniors, who found him a patient and understanding listener."

R. B. W. adds:

"With the passing of Murray Newton the West of Scotland has lost a fine surgeon and an admired and respected man. He was much more than a consultant surgeon: he was regarded as a father confessor by his colleagues, junior and senior, surgical and medical. All brought their problems—professional and even social and domestic—to him knowing they would receive a patient hearing, a sane appraisal, and all the forthright advice and assistance that he could give.

"Essentially conservative in attitude and outlook 'T. M. N.' was a neat and skilful surgeon but could be bold and radical when the occasion demanded. He made a special study of the surgery of goitre and was a pioneer in Scotland of the Böhler techniques of fracture treatment. Although he did not contribute to surgical literature he was an ardent student of it. His teaching of undergraduate students was sound and aimed at inculcating the principles of proper professional conduct and producing graduates who would make good doctors. He clung to the highest ideals professional and ethical, and his integrity and high sense of duty won him the respect and affection of all. His handling of patients, relatives, tissues, and examinees all bore the stamp of the true surgeon—gentle, deft, firm.

"T. M. N. was a champion of the younger men in the profession, especially those whose careers had been interrupted by war service. At the inception of the National Health Service he strove energetically on many committees to ensure that professional standards and rights were not impaired. No lover of bureaucracy and passionately opposed to a whole-time salaried service, few did more than he to ensure that the great experiment of the National Health Service got off to a fair start.

"But it will be as a man that T. M. N. will be remembered, a man of four loves: justice, his profession, his family, and fishing. Any cause, great or small, if it was a just one, had his unstinted and energetic support. Only those privileged to work close to him realised how heavily he leaned on his devoted life partner Janie, whose loving care and affection sustained him through the many ordeals and setbacks of the last ten years. Fishing was his hobby and relaxation. To see the impish glint in his eyes on a forenoon when he had arranged to play truant and go for an afternoon's fishing was an unforgettable insight into the essential goodness and humanity of this beloved man."

Mr. Newton is survived by his wife, two daughters, and two sons who are both in general practice.

TOM HARE

M.D, B.V.Sc. Lpool, M.R.C.V.S.

THOUGH keenly interested in medical affairs, Professor Hare, whose death we announced in our last issue, spent most of his life in investigation of disease in animals. In the veterinary profession he was perhaps best known for his work on beta-hæmolytic streptococcal infection.

He was born in 1895, and he was educated at Loughborough Grammar School. During the 1914–18 war he held a commission with the Cheshire Regiment, and after he was demobilised he studied medicine and veterinary science at Liverpool University. He held fellowships in the department of pathology there before he was appointed in 1927 to the chair of pathology at the Royal Veterinary College, London. From 1934 to 1940 he was director of the Veterinary Research Laboratories.

J. McC., who was his friend for more than thirty years, writes:

"Tom Hare was unique, to many he was an enigma. He combined the dreamy faraway air of a philosopher, the courtly grace of the Regency, the rigorous integrity of a Victorian, and the acute brain of a modern scientist who annotated only in terms of proved fact. Sometimes our views would clash; more often we fought battles together, for he was a courageous and tenacious fighter in any cause which his conscience willed him to espouse. He had no time for, or patience with, bureaucracy or caucus; and all his professional life he fought for the common man as represented by the medical or veterinary practitioner. He gave no thought to any effect that his actions might have on his own personal life or finances when once he had decided to enter the lists. One might expect such a doughty fighter to be of good health and physique; but Hare, though of fair height, was never, in my memory, a fit man. He was spare of frame and walked with a stoop caused by chronic chest trouble, for he had been gassed in the 1914–18 war.

"By upbringing, family connections, and conviction he was a good churchman, and he gave much of his time to church and charitable affairs. He was intensely interested in men and their affairs. In his youth he was in the top class in tennis and of county standard in cricket. Like his father he was interested in archæology and antiques, and he loved to show his friends around his beloved St. Albans. He was a keen student of all things appertaining to natural history and often spent his leisure meandering around the Hertfordshire countryside. He was a good host and loved to entertain his friends at Holywell Hill, and for many years the Herts and Bedfordshire Veterinary Society held their meetings in his house."

Another colleague, A. B. O., recalls Hare's firm conviction of the dignity of the veterinary profession:

"As he once put it to me, 'you are the servant of the man who called you in', and that position enhanced rather than detracted from the dignity of your calling. Furthermore, your relationship was confidential and nothing must be allowed to undermine this. His case-records, always written up if possible immediately after each examination, were models of conciseness and completeness and invariably included a detailed case-history, often obtained only by patient and painstaking questioning. His lifelong hobby of ornithology led naturally to his interest in the diseases of birds.

"He had the true artist's love for things of beauty, and was a collector of antique glass and china on which he could speak with obvious pleasure and authority. For some time before his last illness he had been working on a life of Harvey, and we often spent our lunch hour talking about it. The time and trouble he would give to checking a fact or a date was remarkable. Perhaps sincerity would most aptly sum up his character. This, together with his belief in the Christian way of life, made him uncompromising on matters of principle, and forthright in condemning indifference and selfishness. Though he appreciated and admired traditional ceremony he shrank from personal ostentation, and the many offers of help and encouragement I can recall over the past thirty years were

always made with tact and sympathy. To many of us his death means the absence of an admired and trusted friend; to the veterinary profession as a whole it means the loss of a staunch and untiring champion."

Professor Hare, who died on March 20, leaves a widow, one son, and four daughters.

ERNEST DAVIS RUTHERFORD
M.B. R.U.I.

Surgeon Captain E. D. Rutherford died at his home at Newcastle, Co. Down, on March 7, at the age of 81.

His father was Dr. Robert Rutherford, who practised at Manorhamilton, Co. Leitrim, for over 50 years. He was educated at Portora Royal School, Enniskillen, and studied medicine at Queen's College, Belfast, graduating M.B. from the Royal University of Ireland in 1902. After doing a few trips as surgeon in the Bibby Line he entered the Royal Navy in 1904, and he served at Haslar Hospital, in Malta, and the Far East. During the 1914–18 war he did pioneer work on asdic equipment, and for his services to Greek civilians he was decorated by the King of the Hellenes with the Order of the Redeemer.

After retiring from the Navy in 1922 he took a postgraduate course in electrotherapy at St. Thomas's Hospital. Later he practised in that specialty in Belfast, holding an honorary appointment at the Royal Victoria Hospital. During the late war he was recalled to the Navy to hold shore appointments at the Admiralty and in H.M.S. *Excalibur* at Alsager. He retired at the end of 1944. He leaves a widow and one son.

Dr. PHILIP HAMILL

An old friend and colleague writes:

"Philip Hamill was, I believe, a member of the staff of St. Andrew's Hospital, Dollis Hill, from its opening, and he served it devotedly for many years. He was also on the staff of the National Hospital for Diseases of the Heart, and he had a considerable reputation in cardiology before it became a rather closed specialty. He had in his consulting-room one of the early and more primitive electrocardiographs. For many years we held our outpatient sessions on the same day in adjoining rooms, and I learned to appreciate Hamill's practical efficiency in his clinical work. He gave a great deal of thought and trouble to the management of simple as well as difficult cases, and he was ever anxious to ensure that small details of treatment and care which might help the patient's recovery or add to his comfort were meticulously carried out. No trouble or personal inconvenience could affect his desire to help, comfort, and sustain his patients. His friends, and especially his younger colleagues, often turned to him for advice, and they always found him constructively helpful and never destructively critical. His essential kindliness was shown by the practical aid he so readily offered those who were starting their careers. A learned physician, a first-class doctor, and a good friend has left us."

Diary of the Week

APRIL 5 TO 11

Wednesday, 8th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Sir Clement Price Thomas: Conservative and Extensive Resection for Carcinoma of the Lung. (Tudor Edwards lecture.)

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (18, Nicolson Street.) Prof. Robert Cruickshank: Acute Respiratory Infections in Childhood.

Thursday, 9th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Mr. T. J. S. Patterson: Congenital Deformities of the Hand. (Hunterian lecture.)

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM
9 A.M. (1, Wimpole Street, W.1.) Opening of three-day meeting.

Friday, 10th

MEDICAL RESEARCH COUNCIL
5 P.M. (National Institute for Medical Research, The Ridgeway, N.W.7.) Dr. S. E. Luria (Cambridge, Mass.): Mechanisms of Infective Heredity in Bacteria.

Saturday, 11th

FACULTY OF RADIOLOGISTS
9.45 A.M. (Western Infirmary, Glasgow, W.1.) Symposium on Cerebral Tumours (opening of one-day meeting).

Notes and News

THE MEDICAL SICKNESS SOCIETY

FOR the first thirty-five years after its foundation in 1884, the Medical Sickness Society was no more than a small friendly society, with a membership slowly growing from the original 400 to about 3000. Since 1920, when it became a mutual insurance company, the picture has changed: by its fiftieth anniversary it had 7000 members and funds of £1 million, and it had developed the practice of declaring bonuses on sickness policies—which is done by no other insurance company. Its funds now exceed £8 million, belonging to over 18,000 members.

At the seventy-fifth anniversary dinner, held at the Apothecaries Hall on March 20, Lord Evans said that the society, founded by doctors for doctors, was also run by doctors: except for Mr. Bertram Sutton, who entered its service in 1899 and was long its chief officer, all the board were members of the medical and dental professions. Both to Mr. Sutton and to Mr. E. A. J. Heath, who succeeded him fourteen years ago, the board owed a great debt. Finally, in speaking of the chairman, Mr. McNeill Love, Lord Evans recalled Sydenham's saying that he had "weighed in a nice and scrupulous balance whether it is better to serve men or be praised by them." Like Sydenham, Robbie Love preferred the former.

Mr. Love said that, of the many insurance companies founded last century to meet the needs of a particular trade or vocation, the Medical Sickness Society was the only survivor. Most companies fought shy of guaranteeing sickness benefit indefinitely till the member recovered or the policy expired; but the medical profession had had this for seventy-five years. Through a subsidiary company formed last year (the Permanent Sickness Insurance Company) members of other professions could now have this kind of security, and he hoped they would find it as useful as doctors had done. The society was also celebrating the tenth anniversary of its other subsidiary, the Medical Sickness Finance Corporation, established in 1949 to help doctors and dentists with the purchase of cars and equipment. Though its terms were the most favourable possible, the corporation was flourishing.

Dr. A. H. Douthwaite, proposing The Guests, said he hoped they would all attend the centenary dinner: "and you may take it that when the director of a sickness and life assurance company wishes you good health and long life he really means it." Prof. John Bruce, F.R.C.S.E., responding with appropriate vitality, reflected nevertheless that an accident to his audience would solve the registrar problem.

The society's address is 3, Cavendish Square, London, W.1.

BRITISH VIEWS ON CLINICAL TRIALS

THE rising spate of new drugs, and their increasing potency for good and ill, is drawing attention to the need for controlled clinical trials. A conference on this subject was held in Vienna from March 23 to 27 under the auspices of the Conseil des Organisations Internationales des Sciences Médicales.

About 120 people from 16 European countries attended. As medical statistics have been developed intensively in this country, 17 British scientists and clinicians were invited to open the discussions, under the benign but firm chairmanship of Prof. Bradford Hill.

The topics included the aims, ethics, criteria, design, and organisation of clinical trials, and their special applications to acute infections, tuberculosis, rheumatoid arthritis, coronary thrombosis, and cancer. It is intended to publish the proceedings. Dr. J. F. Delafresnaye, secretary of C.I.O.M.S., organised the conference.

CHARING CROSS HOSPITAL

THE West London Hospital (at present with the board of governors of Hammersmith, West London, and St. Mark's Hospitals) and Fulham and Fulham Maternity Hospitals (at present with the Fulham and Kensington Hospital Management Committee) have been transferred to the board of governors of Charing Cross Hospital. Harrow and Wembley

Hospitals have been transferred from the Charing Cross board of governors to the Harefield and Northwood Group Hospital Management Committee.

FAMILY ALLOWANCES AND NATIONAL INSURANCE ACT, 1959

THIS Act, which received the Royal Assent on March 25, contains the following three provisions based on recommendations of the Franks Committee on administrative tribunals and inquiries:

It removes the requirement that leave must be obtained before an appeal can be brought from a local appeal tribunal under the Industrial Injuries Act to the industrial injuries commissioner.

It provides for claims to family allowances to be determined by the independent authorities appointed under the National Insurance Act—namely, insurance officers, local tribunals, and the commissioner. At present claims are decided by the Minister with appeal to an independent referee.

It gives a right of appeal on a point of law from decisions of medical appeal tribunals (which determine questions as to disablement under the Industrial Injuries Act) to the industrial injuries commissioner, subject to leave.

The two last changes are to operate when the regulations have been made by the Minister of Pensions and National Insurance. The first change is now effective.

A NEW JOURNAL

WE welcome the appearance of the *International Journal of Radiation Biology* [1] as potentially of great worth. It has as its aim "to bring together all interests concerned with the biological effects of ionizing radiations". If it succeeds in this aim and does not become yet another source of abstruse though useful information, then it will be very valuable. The first issue contains an interesting collection of papers ranging from chemical protection against ionising radiations to the report of the 1958 International Congress of Radiation Research at Burlington, Vermont.

University of Cambridge

On March 21 the following degrees were conferred:

M.D.—N. T. Holden, P. B. C. Matthews, J. H. Ross, P. D. Trevor-Roper.
M.B., B.Chir.—R. E. Mackie.
M.B.—J. G. D. Simpson, S. O. Suite.

University of London

On Feb. 25 the degree of M.S. was conferred on D. F. N. Harrison.

University of Leeds

At recent examinations the following were successful:

M.D. (with distinction).—D. A. Cahal.
D.P.H.—F. N. Bamford, Gladys V. Bradshaw, J. L. Evans, Jamesina Felgate, George Firth, T. F. McC. Jackson, R. C. Laverick, D. S. Pickup, Bryan Reffold, D. J. Roberts, C. M. Samuel, Ruth R. Stoakley, Jill C. White.

University of Edinburgh

Dr. R. B. Fisher has been appointed to the chair of chemistry in relation to medicine, in succession to Prof. G. F. Marrian, who resigns in September.

Dr. Fisher, who was born in 1907, has been demonstrator in biochemistry at the University of Oxford since 1935. From 1948 to 1955 he was an editor of the *Journal of Physiology*.

University of Dublin

The following have been awarded the diploma in gynæcology and obstetrics:

J. F. Ackary, S. G. Barr, Rehana Bashir, Jaharlal Basu, M. C. Botha, Ramkarran Kachan, Machupe Mphahlele, G. M. J. Pais, Upendra Ambalal Patel, J. W. Redmond, Sudhir Kumar Seal, Shamim Shabbir, Ba Thein, Sein Tin.

Irish Conjoint Board

The following have been granted the licence of the Irish Royal Colleges:

Ann M. Barnes, Anne B. Cowan, Mary P. Daly, L. P. Grime, Mary C. Ingham, Christine Tomlinson.

1. International Journal of Radiation Biology and Related Studies in Physics, Chemistry and Medicine. Vol, 1, no. 1, January, 1959. Editor: W. M. Dale, M.D., D.SC., Department of Biochemistry, Christie Hospital and Holt Radium Institute, Withington, Manchester, 20. Published by Taylor & Francis Ltd., Red Lion Court, Fleet Street, London, E.C.4. £3 15*s*. per vol. (4 issues); £1 per part.

University of Glasgow

Mr. Roland Barnes has been appointed to the chair of orthopædics.

A graduate of Manchester University, Mr. Barnes was elected fellow of the Royal College of Surgeons in 1933, of the Royal Faculty of Physicians and Surgeons of Glasgow in 1947, and of the Royal College of Surgeons of Edinburgh in 1955. After holding various surgical appointments in Manchester Royal Infirmary from 1930 to 1939, he took charge of the orthopædic centre at the Emergency Medical Services hospital at Winwick, Lancashire, where he served until 1943, and where some thousands of Service and civilian injured came under his supervision and care. He has been a member of the staff of the University of Glasgow since 1943, first as lecturer and since 1951 as reader in orthopædics, and has during this period been in charge of the department of orthopædics in the Western Infirmary.

Dr. Thomas Anderson has been appointed to the chair of infectious diseases.

A graduate of Glasgow University, Dr. Anderson was elected fellow of the Royal College of Physicians of Edinburgh in 1940 and of the Royal Faculty of Physicians and Surgeons of Glasgow in 1947. He has held various medical posts in the city and was appointed in 1946 as visiting physician of Knightswood Hospital and consultant in infectious diseases, and concurrently as university lecturer (since 1951 reader) in infetious diseases. Since 1951 he has been in charge of the department of infectious diseases at Ruchill Hospital.

Royal College of Surgeons of England

On Wednesday, April 8, Sir Clement Price Thomas will give a Tudor Edwards lecture. He will speak on conservative and extensive resection for carcinoma of the lung. On Friday, May 22, Lord Cohen of Birkenhead will give a Charles Tomes lecture. His subject will be facial neuralgias. Both lectures will be given at the college, Lincoln's Inn Fields, London, W.C.2, at 5 P.M.

Wessex Regional Hospital Board

At the first meeting of this new board on March 16, Dr. John Revans was appointed senior administrative medical officer.

Dr. Revans, who is 47 years of age, studied medicine at the Middlesex Hospital, where he won the Broderip scholarship and forensic medicine prize. After qualifying in 1935 he held three house-appointments there before joining the Indian Medical Service. He won the Montefiore prize at the Royal Army Medical College in 1936. During the war he served at G.H.Q.'s Middle East and India, and as A.D.M.S. War Staff at the India Office. He was appointed M.B.E., officer of the Order of St. John, and mentioned in despatches. He retired in 1946 from the I.M.S. with the rank of colonel. From 1946 to 1948 he was an assistant secretary of the British Medical Association and in that year he became assistant S.A.M.O. to the South West Metropolitan Regional Hospital Board, being promoted to deputy S.A.M.O. in 1951. He is at present chairman of the advisory panel on central sterile supplies of the Nuffield Provincial Hospitals Trust.

Dinner to Mr. Dickson Wright

A dinner in honour of Mr. A. Dickson Wright was held in London on March 21 by housemen and registrars who have served under him at St. Mary's Hospital. Mr. C. P. Sames presided.

Dr. Paul Wood will speak on modern auscultation at a meeting of the Yorkshire Thoracic Society at 7 P.M. in Leeds General Infirmary on Friday, April 17 (not at 5.30 P.M. as previously announced).

On March 21 the University of Pretoria conferred the honorary degree of M.D. on Dr. G. B. Dowling. During his visit to South Africa, which is sponsored by the British Council, Dr. Dowling will lecture at the Universities of Bloemfontein, Witwatersrand, Cape Town, Stellenbosch, and Durban, and at the South African dermatology congress at Johannesburg.

CORRIGENDUM: *Quantitative Antiobiotic Sensitivity Tests.*—We unfortunately omitted the following acknowledgment from Mr. Zador's letter of March 28: "I wish to express my thanks to the Sheppard Electronic Co. Ltd. for putting the automatic recording apparatus at my disposal".

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